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Theories of the Biogenesis of Flavonoid Compounds.
T. A. GEISSMAN AND ELLY HINREINER 77

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THE BOTANICAL REVIEW

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THEORIES OF THE BIOGENESIS OF FLAVONOID COMPOUNDS

(PART I)

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INTRODUCTION

The intriguing question of the chemical mechanisms by means of which the higher plants synthesize the multitude of compounds found in their roots, bark, leaves, flowers and seeds has been the subject of speculation since the beginnings of the systematic study of organic chemistry. Schemes have been devised to account for the synthesis of carbohydrates (Gardner, 1943), terpenes and isoprenoid compounds (Bogert, 1932; Hall, 1933; Ganapathi, 1937; Tobolsky et al., 1947), alkaloids (Henry, 1949), rubber (Bonner, 1949), steroid sapogenins (Marker, 1947) and other classes of compounds. In addition, theories have been advanced

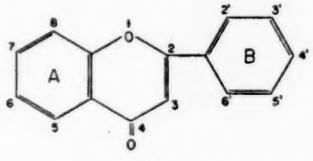
to explain the origin of special structural features, such as the methoxyl group (Browne and Phillips, 1935), the six-carbon moiety of aromatic substances (Hall, 1937) and the flavone structure (Ullal, Shah and Wheeler, 1940).

Certain of these theories are faulty or unsatisfactory in that they represent synthetic routes to structures later shown to be in error (Emde, 1931), or are highly artificial in assuming the presence in the cell of synthetic raw materials or the occurrence in the cell of reactions not known in nature. Some, however, not only possess a high degree of plausibility but have been of great value in suggesting experimental approaches to the general problem and in selecting a probable structure when degradative methods have progressed to a point short of the final elucidation of a structure, have given results which can be satisfied by more than one structure (Robinson, 1948), or have led to the proposal of a structure to which a plausible biosynthesis would lend support (Woodward, 1948). It is the aim of theories of biogenesis not only to make it possible to reach an understanding of the natural synthetic processes of the living cell, but also to make possible predictions which can short-cut the lengthy and often tedious analytical procedures of classical organic chemistry.

The study of the problem of biogenesis can be approached in several ways. The direct experimental approach, in which specific precursors can be furnished to a living organism capable of transforming them into recognizable products, has been applied with conspicuous success in the case of bacteria and fungi (Beadle, 1949) and in a limited way with respect to higher plants (Klein and Linser, 1932). Such studies in higher plants are often likely to give information about only the early stages of the utilization of a nutrient substance, as, for example, in studies of the influence of the structure of different sugars upon the formation of pigments in aquatic plants (references given in Thimann and Edmondson, 1949). It is now recognized that many substances, when fed to an isolated organ, a tissue culture or a plant, may enter the metabolic organization by an initial transformation into simpler substances, and become a part of the common "synthetic pool" of carbon compounds which are then utilized in the synthesis of complex tissue constituents. There is at the present time no appreciable body of experimental evidence from which

can be drawn conclusions regarding the details of the final stages of the elaboration of compounds containing aromatic rings, methoxyl and methylenedioxy groups, and unique structural elements of other kinds. In the absence of such direct evidence it is necessary to examine the problem by what has been termed a "comparative anatomy" of the organic compounds under scrutiny (Schöpf, 1934). In order to do this effectively it is necessary to have for consideration a group of substances so closely related in their main structural features as to suggest their interrelationship either through their common origin or through processes in which a few "parent" substances may be converted by superficial changes into numerous others.

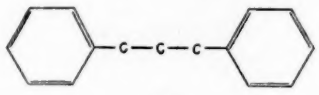
One such class of compounds is that represented by the anthocyanin pigments and the so-called "anthoxanthin" constituents of plants. These constitute the "flavonoid" compounds, so-called because they possess the carbon skeleton of flavone (I):



I

Flavonoid compounds are conveniently designated by the somewhat broader term "C_6-C_3-C_6-compounds", since they are composed of two six-carbon fragments joined by a chain of three carbon atoms. The latter designation has some special advantages, for it brings out clearly the relationship, which will be considered in this review, of the flavonoid compounds to substances possessing only the C_6-C_3-fragment. All of these compounds are widely distributed, as a class, in the higher plants, a circumstance which suggests that they owe their formation to certain processes fundamental to most higher plants. It is with these basal processes that theories of biogenesis can most profitably be concerned; the more superficial aspects of flavonoid structures—the position and nature of sugars glycosidically linked, the degree of methylation of aromatic hydroxyl groups, the presence of acyl residues in ester linkages—will be regarded as separate questions, to be dealt with only insofar as they serve to illustrate further generalizations.

Taking as the basis for the discussion the basic C_6-C_3-C_6-unit (II), in most cases containing two aromatic residues,



II

the chief questions to be considered will be two: (*a*) the number and position of hydroxyl groups in the aromatic rings, and (*b*) the degree and nature of oxidation in the C_3-fragment. The problem then is seen to be primarily one of the oxidation level of the fundamental skeleton.

The kinds of compounds which in the opinion of the authors need to be included in a discussion of the question of flavonoid biogenesis are the following:

A. Benzene derivatives, without side-chains
B. C_6-C_1-, C_6-C_2-, C_6-C_3-compounds, including those which may be regarded as being dimers of these (e.g., lignanes as $(C_6$-$C_3)_2$)
C. C_6-C_n, where $n>3$
D. Chromones other than 2-arylchromones (C_6-C_4)
E. Flavonoid compounds (C_6-C_3-C_6)
    1. Flavonols
    2. Flavones
    3. Benzalcoumaranones
    4. Flavanonols
    5. Flavanones
    6. Chalcones
    7. Anthocyanidins
    8. Dihydrochalcones
    9. Catechins
F. Isoflavones (C_6-C_3-C_6)
G. Xanthones and benzophenone derivatives (C_6-C-C_6)
H. Stilbenes (C_6-C_2-C_6)
I. Brazilin and hematoxylin (C_6-C_3(C)-C_6)

and variations of the following kinds:

J. Compounds of the above classes containing
    1. Furo-rings

2. Chromano-rings
3. β,β-Dimethylallyl ("prenyl") side-chains
4. Modified and vestigial isoprenoid side-chains of other kinds.

In the following section will be presented a review of the known naturally-occurring compounds of the classes listed above. The significant structural relationships which exist between these classes and between members of each class will be pointed out and will serve as the basis for the later discussion of their possible biosynthetic origin.

NOTE: The number assigned to each of the compounds listed in tables in the following section will be used throughout the discussion, and will be found in parentheses following the name whenever the compound is referred to.

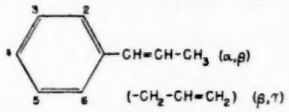
A SURVEY OF NATURALLY-OCCURRING FLAVONOID AND RELATED SUBSTANCES PERTINENT TO THIS DISCUSSION

The large C_6-C_3 class of compounds appears to occupy a central position in a discussion of the biogenesis of the various sorts of natural substances to be dealt with in this review. It is therefore convenient and appropriate to consider them at the outset, even before surveying the simpler C_6-, C_6-C_1-, and C_6-C_2-classifications. The basic compounds of this group are those having an unsaturated, three-carbon, aliphatic side-chain attached to an aromatic, hydroxyl-substituted ring (the propenylbenzenes), and their derivatives in which the side-chain is varied by the presence of an alcohol, carbonyl or carboxyl function. This basic skeleton is modified further in the coumarins and lignanes by cyclization and other condensations.

PROPENYLBENZENES

The propenylbenzenes (Table 1) are widespread among the families of angiosperms and are usually isolated from the essential oils of these plants. The double bond, though readily isomerized in the laboratory to the α,β-position (i.e., in conjugation with the benzene ring), exists in nature more commonly in the β,γ-position. However, asarone (18) and isoeugenol methyl ether (11), both of which are found in species of *Asarum;* isoeugenol (7) and isosafrole (13), which occur together in ylang-ylang oil from *Cananga odorata;* and anethole (3), isoapiole (22) and foeniculin (4),

TABLE 1. NATURALLY-OCCURRING PROPENYLBENZENES



Compound	Substituents	Sources
1) Chavicol	(β,γ) 4-hydroxy	*Piper betle* (Piperaceae); *Zingiber officinale* (Zingiberaceae); *Barosma venustum* (Rutaceae); *Pimenta acris* (Myrtaceae); and other plants
2) Esdragol	(β,γ) 4-methoxy	*Illicium verum* (Magnoliaceae); *Pimpinella anisum, Foeniculum vulgare* (Umbelliferae); *Collinsonia anisata, Ocimum minimum, O. menthaefolium* (Labiatae); and other plants
3) Anethole	(α,β) 4-methoxy	*Piper peltatum* (Piperaceae); *Illicium religiosum, I. verum* (Magnoliaceae); *Canarium commune* (Burseraceae); and other plants
4) Foeniculin	(β,γ) 4-isopenteny-loxy	*Foeniculum vulgare* (Umbelliferae); *Illicium religiosum* (Magnoliaceae)
5) Allylpyrocatechol	(β,γ) 3,4-dihydroxy	*Piper betle* (Piperaceae)
6) Eugenol	(β,γ) 3-methoxy-4-hydroxy	*Eugenia caryophyllata* (Myrtaceae); and other plants
7) Isoeugenol	(α,β) 3-methoxy-4-hydroxy	*Michelia champaca* (Magnoliaceae); *Cananga odorata* (Anonaceae); *Myristica fragrans* (Myristicaceae); *Cinnamomum pedunculatum, Nectandra puchurymajor* (Lauraceae)
8) Acetyleugenol	(β,γ) 3-methoxy-4-acetoxy	*Cinnamomum ceylanicum, Laurus nobilis* (Lauraceae); *Eugenia caryophyllata* (Myrtaceae)
9) Chavibetol	(β,γ) 3-hydroxy-4-methoxy	*Piper betle* (Piperaceae)

TABLE I (*continued*)

Compound	Substituents	Sources
10) Eugenol methyl ether	(β,γ) 3,4-dimethoxy	*Piper betle, P. angustifolium* (Piperaceae); *Cinnamomum pendunculatum, C. camphora, Umbellularia californica* (Lauraceae); *Pimenta officinalis, P. acris* (Myrtaceae); and other plants
11) Isoeugenol methyl ether	(α,β) 3,4-dimethoxy	*Cymbopogon javanensis* (Gramineae); *Asarum arifolium* (Aristolochiaceae)
12) Safrole	(β,γ) 3,4-methylenedioxy	Essential oils from *Cananga odorata* (Anonaceae); *Illicium religiosum* (Magnoliaceae); numerous species of *Cinnamomum* (Lauraceae); and other plants
13) Isosafrole	(α,β) 3,4-methylenedioxy	*Illicium religiosum* (Magnoliaceae); *Cananga odorata* (Anonaceae)
14) Elemicin	(β,γ) 3,4,5-trimethoxy	*Cymbopogon procerus* (Gramineae); *Cinnamomum glanduliferum* (Lauraceae); *Boronia pinnata* (Rutaceae); *Canarium luzonicum* (Burseraceae); *Backhousia myrtifolia* (Myrtaceae)
15) Myristicin	(β,γ) 3-methoxy-4,5-methylenedioxy	*Monodora myristica* (Anonaceae); *Myristica fragrans* (Myristicaceae); *Cinnamomum glanduliferum* (Lauraceae); *Petroselinum sativum, Anethum graveolens* (Umbelliferae)
16) Isomyristicin	(α,β) 3-methoxy-4,5-methylenedioxy	*Myristica fragrans* (Myristicaceae); *Anethum graveolens* (Umbelliferae)
17) Croweacin	(β,γ) 2-methoxy-3,4-methylenedioxy	*Eriostemom crowei* (Rutaceae)
18) Asarone	(α,β) 2,4,5-trimethoxy	*Acorus calamus, A. gramineus* (Araceae); *Piper angustifolium* (Piperaceae); *Asarum europaeum, A. arifolium* (Aristolochiaceae); *Daucus carota* (Umbelliferae)

TABLE 1 (*continued*)

Compound	Substituents	Sources
19) Allyltetramethoxybenzene	(β,γ) 2,3,4,5-tetramethoxy	French parsley-seed oil (*Petroselinum sativum*, Umbelliferae)
20) Apiole	(β,γ) 2,5-dimethoxy-3,4-methylenedioxy	*Piper angustifolium* (Piperaceae); *Ocotea* spp. (Lauraceae); *Petroselinum sativum* (Umbelliferae)
21) Dill-apiole	(β,γ) 2,3-dimethoxy-4,5-methylenedioxy	*Piper angustifolium* (Piperaceae); *Crithmum maritimum*, *Anethum graveolens*, *A. Sowa* (Umbelliferae)
22) Isoapiole	(α,β) 2,3-dimethoxy-4,5-methylenedioxy	*Crithmum maritimum*, *Anethum graveolens* (Umbelliferae)

which have been isolated from *Foeniculum* and other Umbelliferae, possess the α,β-double bond.

Except for the compounds having only one oxygen atom, all of the propenylbenzenes have hydroxyl substituents * in the 3- and 4-positions of the ring; where there is only one such substituent, it invariably occupies the 4-position. The 3,4-dihydroxy pattern is modified by every possible combination of methoxylation, and also by methylenedioxy ring formation; the 3,4-dihydroxy derivative, allylpyrocatechol (5), is found in betel-leaf oil; 3-methoxy-4-hydroxyallybenzene, or eugenol (6), is a constituent of oil of cloves, and many other essential oils; its isomer, chavibetol (9), having the less frequently-encountered 3-hydroxy-4-methoxy configuration, has been isolated from *Piper betle*. (The cinnamic acid derivative, isoferulic acid (42); the stilbene, rhapontin (314); the flavanone, hesperidin (248); the flavone, diosmin (197*a*); and the isocoumarin, phyllodulcin (LVI), appear to be the only other

* In discussing the hydroxylation patterns of the C_6-rings in this review, the term "hydroxyl group" or "hydroxyl substituent" is used in the generic sense and is meant to include substituted hydroxyl groups such as methoxy, methylenedioxy and glycosylated hydroxyl groups, and the heterocyclic oxygen atom in flavones, anthocyanins, etc.

The presence of such substituents on a benzene nucleus does not affect the classification of such a ring as a C_6-structure, since such classification is based upon the fundamental carbon skeleton. For example, catechol (*o*-dihydroxybenzene) and its dimethyl ether, veratrol, are both regarded as C_6-compounds, even though the latter has the empirical formula, $C_8H_{10}O_2$.

cases in which a 3-hydroxy-4-methoxyphenyl group is known to occur; the isomeric 3-methoxy-4-hydroxyphenyl nucleus, on the other hand, is one of the most typical structures encountered among natural products.) The dimethoxy compound, eugenol methyl ether (10), and the methylenedioxy derivative, safrole (12), are both well-known compounds of widespread occurrence.

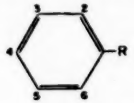
Several of the propenylbenzenes have additional hydroxylated or methoxylated positions. Although there are isolated examples of such compounds in a number of families (see Table 1), the occurrence of polyhydroxy derivatives seems to be most frequent among the Umbelliferae. Myristicin (15) and apiole (20) from parsley oil, dill-apiole (21) from *Anethum,* and isoapiole (22) from *Crithmum maritimum* are methoxylated derivatives of safrole and isosafrole, while 2,3,4,5-tetramethoxyallylbenzene (19) from French parsley oil shows a closely-related structure in which the methylenedioxy ring is opened.

Another interesting and unusual allylbenzene derivative produced by an umbelliferous species is foeniculin (4). It is the isopentenyl ether of chavicol, and was isolated from fennel oil. The isopentenyl moiety with its obvious relationship to isoprene is of considerable significance to the biogenesis of natural products. Many, indeed probably most, naturally-occurring coumarins, particularly those present in members of the Umbelliferae, bear isopentenyl or modified isopentenyl substituents; structures based on this characteristic five-carbon, branched-chain skeleton are found among the members of practically all of the other classes of naturally-occurring compounds as well.

ALCOHOLS, ACIDS AND CARBONYL COMPOUNDS OF THE C_6-C_3-CLASS

The C_3-side-chain exists in several other oxidation states in various naturally-occurring derivatives of cinnamyl alcohol, cinnamaldehyde and cinnamic acid (Table 2). The glucosides, coniferin (25*a*) and syringin (27), which are di- and trihydroxy derivatives, respectively, of cinnamyl alcohol, show an interesting taxonomic relationship. The former is a common constituent of the cambial sap of both gymnosperms and angiosperms, while the latter is found only in that of angiosperms. It has also been observed that degradation of the lignin of gymnosperms produces fragments having the coniferyl (or vanillyl) nucleus, while similar

TABLE 2. NATURALLY-OCCURRING DERIVATIVES OF C_6-C_3- ALCOHOLS, ALDEHYDES, KETONES AND ACIDS



Compound	Substituents	Sources
23) Cinnamyl alcohol	(R=CH=CHCH$_2$OH)	Esterified with cinnamic acid in *Styrax* spp. (Styraceae); *Myroxylon Pereirae* (Leguminosae); *Cinnamomum ceylonicum* (Lauraceae); *Hyacinthus orientalis*, *Xanthorrhoea hastilis* (Liliaceae); and other plants
24) Phenylpropyl alcohol (Dihydrocinnamyl alcohol)	(R=CH$_2$CH$_2$CH$_2$OH)	As the cinnamate in *Styrax* spp., *Myroxylon Pereirae*; and other plants
25) Coniferyl alcohol	3-methoxy-4-hydroxy (R=CH=CHCH$_2$OH)	.....
25*a*) Coniferin	4-glucoside of coniferyl alcohol	Cambial sap of *Larix europaea*, *Picea excelsa* and other Pinaceae; *Vanilla planifolia* (Orchidaceae); *Styrax* spp. (Styraceae); and other plants
25*b*) Lubanol benzoate	benzoyl ester (aliphatic hydroxyl) of coniferyl alcohol	*Styrax* spp. (Styraceae)
26) Cubebin	3,4-methylenedioxy (R=CH=CHCH$_2$OH)	*Piper cubeba* (Piperaceae)
27) Syringin	3,5-dimethoxy-4-glucosoxy (R=CH=CHCH$_2$OH)	Bark of *Syringa vulgaris* and *Ligustrum vulgare* (Oleaceae); *Robinia pseudacacia* (Leguminosae); and other plants

TABLE 2 (*continued*)

Compound	Substituents	Sources
28) Cinnamaldehyde	(R = CH=CHCHO)	*Cinnamomum ceylanicum, C. cassia, C. mindandense,* etc. (Lauraceae); *Altingia excelsa* (Hamamelidaceae); *Hyacinthus orientalis* (Liliaceae); and other plants
29) Phenylpropionaldehyde (Hydrocinnamaldehyde)	(R = CH_2CH_2CHO)	*Cinnamomum ceylanicum, C. cassia* (Lauraceae)
30) *o*-Methoxycinnamaldehyde	2-methoxy (R = CH=CH=CHO)	*Cinnamomum cassia*
31) *p*-Methoxycinnamaldehyde	4-methoxy (R = CH=CHCHO)	*Artemisia dracunculus* (Compositae)
32) Anise ketone	4-methoxy (R = CH_2COCH_3)	*Illicium verum* (Magnoliaceae); *Pimpinella anisum, Foeniculum vulgare* (Umbelliferae)
33) Cinnamic acid	(R = CH=CHCOOH)	Free and esterified in many resins and essential oils; *Kaempferia Galanga, Alpinia nutans* (Zingiberaceae); *Cinnamomum ceylanicum, C. cassia* (Lauraceae); *Liquidambar orientale* (Hamamelidaceae); *Xanthoxylum acanthopodium* (Rutaceae); and other plants
34) Hydrocinnamic acid (β-Phenylpropionic acid)	(R = CH_2CH_2COOH)	As the acetoester in the oil from *Cassia* spp. (Leguminosae)
35) Melilotoside	2-glucosoxy (R = CH=CHCOOH)	Flowers of *Melilotus altissimus, M. arvensis* (=*M. officinalis*) (Leguminosae)
36) *p*-Coumaric acid (*p*-Hydroxycinnamic acid)	4-hydroxy (R = CH=CHCOOH)	*Picea excelsa* (Pinaceae); various species of *Aloë* (Liliaceae); *Hedychium spicatum* (Zingiberaceae); *Daviesia latifolia, Melilotus officinalis, M. altissimus, Trifolium pratense* (Leguminosae); and other plants

TABLE 2 (*continued*)

Compound	Substituents	Sources
37) Melilotic acid (Hydrocoumaric acid)	4-hydroxy ($R=CH_2CH_2COOH$)	*Melilotus officinalis, M. altissimus* (Leguminosae); *Nicotiana tabacum* (Solanaceae)
38) *p*-Methoxycinnamic acid	4-methoxy ($R=CH{=}CHCOOH$)	As the ethyl ester in various species of *Aloë* (Liliaceae); *Hedychium spicatum, Kaempferia Galanga* (Zingiberaceae)
39) Caffeic acid	3,4-dihydroxy ($R=CH{=}CHCOOH$)	*Papaver somniferum* (Papaveraceae); *Conium maculatum* (Umbelliferae); *Digitalis purpurea* (Scrophulariaceae); and other plants
40) Hydrocaffeic acid	3,4-dihydroxy ($R=CH_2CH_2COOH$)	Leaves of *Beta vulgaris* (Chenopodiaceae)
41) Ferulic acid	3-methoxy-4-hydroxy ($R=CH{=}CHCOOH$)	*Opopanax chironium, Ferula foetida* (Umbelliferae); probably in the exuded resin of *Pinus laricio* and *Larix europaea* (Pinaceae)
42) Isoferulic acid	3-hydroxy-4-methoxy ($R=CH{=}CHCOOH$)	Rhizomes of *Cimicifuga racemosa* (Ranunculaceae)
43) Sinapin	4-hydroxy-3,5-dimethoxy ($R=CH{=}CHCOOCH_2CH_2{-}N(CH_3)_3OH$)	Seeds of black mustard (*Brassica nigra*, Cruciferae)

treatment of the lignin of angiosperms gives the same degradation products along with their counterparts having the syringyl skeleton.

The close biosynthetic relationship of the various C_6-C_3-classes is clearly indicated by several examples of the co-existence in the same species or genus of two or more compounds having identical substituents on their aromatic nuclei. Cinnamic acid (33) occurs esterified with the structurally-related cinnamyl alcohol (23) or its dihydro derivative, phenylpropyl alcohol (24), in the resins from *Styrax* and several other tropical genera. Cinnamaldehyde (28) as well as esters of cinnamic acid are found in the various species of *Cinnamomum*. *o*-Methoxycinnamaldehyde (30) is present occasionally also in the oil from *Cinnamomum cassia*. A 3,4-methylenedioxy substituent is characteristic of many of the compounds isolated from the genus *Piper*. *Piper cubeba* yields a cinnamyl alcohol derivative (26) and a lignane (49), both of which are called cubebin, having this moiety. From other species of *Piper* piperic (167*a*) and isochavicic acids (167*b*), and the lactone, methysticin (171), are derived; all of these also have a methylenedioxy ring. In the propenylbenzene, dill-apiole (21), which occurs in *Piper angustifolium* as well as dill-oil, two methoxyl groups are substituted on the aromatic ring in addition to the 3,4-methylenedioxy ring.

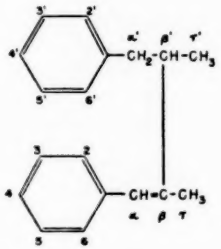
Other simple C_6-C_3-acids, alcohols and carbonyl derivatives also tend to follow the usual hydroxylation patterns; i.e., a single hydroxy substituent almost always occupies the 4-position, while with two or more such substituents, the 3- and 4-positions are filled.

LIGNANES

The lignanes (Table 3) are dimeric derivatives of the C_6-C_3-class of compounds. The linkage occurs at the β-carbons of the side-chains, and the hydroxylation pattern of the aromatic nuclei is almost invariably of the 3,4-dihydroxy-substituted type. The variety of oxidation states in which the C_3-fragment may exist in nature is well illustrated by the lignanes. The different oxidation states find expression in double bonds (*l*-guaiaretic acid (44)); hydroxyl groups (*l*-olivil (50), *l*-cubebin (49), *l*-podophyllotoxin (59), *d*-isoolivil (58), *d*-lariciresinol (51), and gmelinol (56));

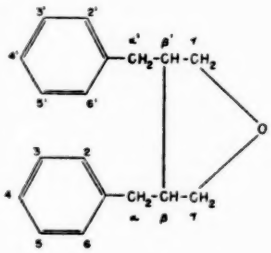
TABLE 3. NATURALLY-OCCURRING LIGNANES

2,3-Dibenzylbutane derivatives:



Compound	Substituents	Sources
44) *l*-Guaiaretic acid	3,3′-dimethoxy-4,4′-dihydroxy	Resin from *Guaiacum officinale* (Zygophyllaceae)
45) Nordihydroguaiaretic acid	3,3′, 4,4′-tetrahydroxy-α,β-dihydro	*Larrea divaricata* (Zygophyllaceae)

Tetrahydrofuran derivatives:



46) *l*-Matairesinol	3,3′-dimethoxy-4,4′-dihydroxy-γ-keto	Heartwood of *Podocarpus spicatus* (Taxaceae)
47) *l*-Arctigenin	3,4,4′-trimethoxy-3′-hydroxy-γ-keto	As the glycoside in the seeds of *Arctium lappa* (Compositae)
48) *l*-Hinokinin	3,4-3′,4′-*bis*methylenedioxy-γ-keto	*Cupressus obtusa* (Pinaceae)
49) *l*-Cubebin	3,4-3′,4′-*bis*methylenedioxy-γ-hydroxy	Fruit of *Piper cubeba* (Piperaceae)

TABLE 3 (*continued*)

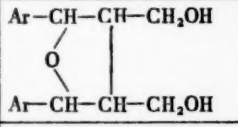
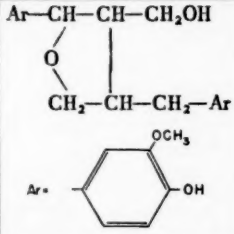
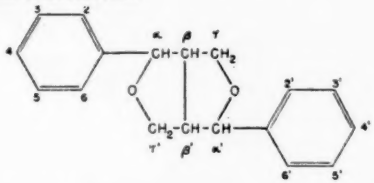
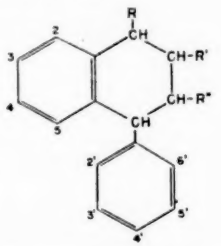
Compound	Substituents	Sources
50) *l*-Olivil		Resin from *Olea europea* (Oleaceae)
51) *d*-Lariciresinol		Resin of *Larix decidua* (Pinaceae)
Furanofuran derivatives: 		
52) *d*-Pinoresinol	3,3′-dimethoxy-4,4′-dihydroxy	Resins of *Picea abies*, *Pinus nigra*, *P. sylvestris* (Pinaceae)
53) *d*-Forsythigenol (*d*-Pinoresinol monomethyl ether)	3,3′,4-trimethoxy-4′-hydroxy	As a glycoside in the leaves of *Forsythia koreana* (Oleaceae)
54) *l*-Eudesmin (Pinoresinol dimethyl ether)	3,3′,4,4′-tetramethoxy	*Eucalyptus hemiphloia* (Myrtaceae)
55*a*) *d*-Sesamin	3,4-3′,4′-*bis*methylenedioxy	Seeds of *Sesamum indicum* (Pedaliaceae)
55*b*) *l*-Sesamin	3,4-3′,4′-*bis*methylenedioxy	*Asarum Sieboldii* (Aristolochiaceae)
55*c*) *l*-Asarinin	(diastereoisomer of *l*-Sesamin)	*Asarum Sieboldii* (Aristolochiaceae)
56) Gmelinol	3,3′,4,4′-tetramethoxy-β-hydroxy	*Gmelina Leichardii* (Verbenaceae)

TABLE 3 (*continued*)

α-Phenyltetralin derivatives:



Compound	Substituents	Sources
57) *l*-Conidendrin (Tsugaresinol)	3,3'-dimethoxy-4,4'-dihydroxy (R=H; R',R"=$COOCH_2$—)	Wood of *Tsuga Sieboldii* and *Picea excelsa* (Pinaceae); *Podocarpus spicatus* (Taxaceae) in small amounts
58) *d-Iso*olivil	3,3'-dimethoxy-4,4'-dihydroxy (R=OH; R'=R"=CH_2OH)	Wood of *Olea Cunninghamii* (Oleaceae)
59) *l*-Podophyllotoxin	3,4-methylenedioxy-3',4',5'-trimethoxy (R'=CH_2OH; R",R=COO—)	Root resins of several species of *Podophyllum* (Berberidaceae)

the formation of furan rings by means of an oxide linkage between the α-carbon atoms of the two C_6-C_3-moieties (*l*-olivil (50)), the two γ-carbon atoms (*l*-cubebin (49)), or the α-atom of one side-chain and the γ-atom of the other (*d*-lariciresinol (51), *d*-pinoresinol (52), *d*-forsythigenol (53), *l*-eudesmin (54), *d*-sesamin (55*a*) and gmelinol (56)); the formation of a lactone between a carboxyl group and a hydroxyl group on different side-chains (*l*-matairesinol (46), *l*-arctigenin (47), *l*-hinokinin (48), *l*-conidendrin (57), and *l*-podophyllotoxin (59)); or in the removal of hydrogen atoms between a side-chain and one of the aromatic rings (*l*-conidendrin (57), *l*-podophyllotoxin (59) and *d*-isoolivil (58)). By virtue of such additional carbon-carbon linkages or oxygen bridges, many of the lignanes, while retaining the fundamental 2,3-dibenzylbutane skeleton, are also derivatives of α-phenyltetralin, α,α'-diphenylfuran, β,β'-dibenzylfuran, butyrolactone or furanofuran.

Haworth (1942) has proposed that the union of two α-propenylbenzene derivatives at the β-carbon atoms results from oxidative coupling of anionoid centers in the side-chain in somewhat the same manner as the oxidation of phenols to peroxides or diphenyl ethers, suggesting that the β-carbon atoms are most capable of acquiring this anionoid character in view of the conjugation with the aromatic ring which permits stabilization of the charge. The oxidation state of the terminal carbon atom of the C_6-C_3-precursor is, of course, unknown, but any of the α,β-unsaturated substances, such as isoeugenol (7), isosafrole (13), coniferyl alcohol (25), ferulic acid (41) or cinnamaldehyde (28), could presumably serve as intermediates. Indeed, considering the variations in the oxidation states of the aliphatic carbon atoms of different lignanes, it is not unreasonable to suppose that more than one type of C_6-C_3-precursor may be involved. Moreover, the extent, as well as the variety, of oxidation of the side-chains (i.e., many of the compounds have oxygen atoms on nearly all of the aliphatic carbon atoms) suggests that the basic precursor of the lignanes is a C_6-C_3-substance in which the C_3-fragment is thoroughly oxidized. A trihydroxy derivative of the type represented by C_6-$CHOHCHOHCH_2OH$, or a hydroxycarbonyl compound such as that proposed for the C_6(B)-C_3-moiety in a later section (Part II), have the sort of oxidized side-chains from which the various carboxyl, carbonyl and hydroxyl functions found in the lignanes could conceivably develop. *l*-Guaiaretic (44) acid and nordihydroguaiaretic acid (45) are the only lignanes with no oxygenated functions in the side-chain. Schroeter (1918) has suggested the derivation in the plant of the former lignane from two moles of isoeugenol (7).

The lignanes, *l*-hinokinin (48) and *l*-cubebin (49), differ only in the oxidation state of one carbon atom, and indeed, the α-hydroxyfuran (cubebin) has been oxidized to the butyrolactone (hinokinin) in the laboratory. There is, however, no evidence to suggest that such a process plays a part in the formation of hinokinin or the other lactonic lignanes in vivo. These compounds may originate by dimerization of like C_6-C_3-fragments, followed by appropriate oxidation and/or reduction of the terminal carbon atoms to produce the alcohol and acid moieties of the lactone; but in view of the occurrence of cinnamoyl esters of phenylpropyl and cinnamyl alcohols in nature, the origin of these lignanes directly

from two C_6-C_3-moieties already joined by an ester linkage, by bond formation between the β-carbons, is equally plausible.

l-Conidendrin (57) resembles *l*-matairesinol (46) except that in the former the α-carbon of one C_6-C_3-unit is bonded to the benzene ring of the other in the ortho position, giving an α-phenyltetralin. *l*-Conidendrin has been found in small amounts in *Podocarpus spicatus,* the conifer from which matairesinol is isolated, suggesting a possible biogenetic relationship between the two lignanes (Haworth, Richardson and Sheldrick, 1935). Other lignanes of the α-phenyltetralin group are *d*-isoolivil (58) and *l*-podophyllotoxin (59). The latter is unusual in that one of its aromatic nuclei carries a methylenedioxy ring and the other is substituted with three methoxyl groups. Although in both *l*-arctigenin (47) and *d*-forsythigenol (53) one benzene ring is a dimethoxy derivative while the other is substituted with one hydroxyl and one methoxyl group, podophyllotoxin is the only known naturally-occurring lignane in which the basic hydroxylation pattern of the two rings is different.

COUMARINS

One of the most important classes of C_6-C_3-structures is that of the coumarins (Table 4). Their distribution is very broad, but they are particularly abundant in the Umbelliferae and Rutaceae. Their relationship to the previously discussed C_6-C_3-compounds is aparent from the prevalence among them of the more typical hydroxylation patterns, as well as the occurrence in the same plant of related compounds of other C_6-C_3-classes. A good example of the latter is the presence of coumarin (60), melilotoside (35) (the glucoside of *o*-hydroxycinnamic acid) and melilotin (61) (dihydrocoumarin) in *Melilotus officinalis. p*-Hydroxyhydrocinnamic acid (37) (melilotic acid) is found esterified with *o*-hydroxycinnamic acid in the same plant.

In the coumarin series also, hydroxy substituents occur most frequently in the position *para* to the side-chain (the 7-position in the coumarin system of numbering) for monohydroxy derivatives (umbelliferone (62), herniarin (63), osthol (67), etc.), and in the *meta* and *para* positions (6,7- or 7,8-positions, depending on the direction of lactone ring-closure) for dihydroxy derivatives (esculin (69*a*), cichoriin (69*b*), daphnin (72)). However, many furo- and chromano-coumarins (for example, bergaptol (83), ostruthol

(87), xanthoxyletin (103)) are hydroxylated in the 5- and 7-positions. Similarly, 6,7,8-hydroxy substitution is fairly general for the simple trihydroxylated coumarins, such as fraxin (77) and fraxidin (79), although among the furocoumarins a 5,7,8-pattern of the sort exemplified by phellopterin (95) and pimpinellin (100) is almost universal. In fact, structures based on phloroglucinol and 1,2,3,5-tetrahydroxybenzene are typical of naturally-occurring coumarones (benzofurans) and chromones in general, whether or not these substances are also coumarin derivatives (cf. Khellin (161) and isoeugenitol (157)).

Examples of the occurrence of structurally-related coumarins together in the same species, genus or family are numerous. Structures having the 7-hydroxycoumarin skeleton are particularly abundant among the Umbelliferae, and 7-hydroxycoumarin itself is so widespread in this family that it is named " umbelliferone ". In the genus *Peucedanum* of the parsley family are found, in addition to umbelliferone, a number of derivatives of umbelliferone which have an isoprenoid * side-chain in the 6- or 8-position. These include the 6-geranyl derivative, ostruthin (65), and 7-methoxy-8-isopentenylcoumarin, or osthol (67), as well as three coumarins, nodakenin (96*a*), peucedanin (82) and athamantin (101), in which an alkyl side-chain of the isopentenyl type is cyclized with the 7-hydroxyl group giving a substituted furan ring. The latter two coumarins are unique in being hydroxylated in the 3-position of the furan ring.

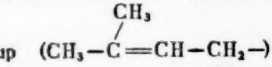
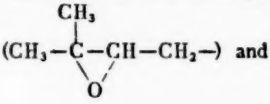
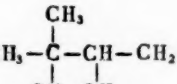
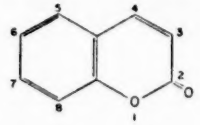
* An isoprenoid group is one based on the five-carbon, branched-chain skeleton of isoprene or a dimer, trimer, etc. of isoprene. In addition to the isopentenyl group  and its simple oxygenated derivatives, such as the epoxide  and the glycol  , the terpenoid and sesquiterpenoid, respectively, geranyl ($(CH_3)_2C{=}CHCH_2{-}CH_2{-}C(CH_3){=}CH{-}CH_2{-}$) and farnesyl ($(CH_3)_2C{=}CH{-}CH_2{-}[{-}CH_2{-}C(CH_3){=}CH{-}CH_2]_2{-}$), side-chains are among the most frequently-encountered isoprenoid groups.

TABLE 4. NATURALLY-OCCURRING COUMARINS



Compound	Substituents	Sources
60) Coumarin	.....	Widely distributed in a great many families
61) Melilotin	3,4-dihydro	*Melilotus officinalis* (Leguminosae)
62) Umbelliferone	7-hydroxy	*Levisticum officinale, Ferula galbaniflua, F. foetida, Peucedanum ostruthium* (Umbelliferae); *Daphne mezereum* (Thymelaeaceae); *Matricaria chamomilla* (Compositae); and other plants
62*a*) Skimmin	7-glucoside of umbelliferone	*Skimmia japonica* (Rutaceae); *Ferula sumbul* (Umbelliferae)
63) Herniarin	7-methoxy	*Herniaria hirsuta, H. glabra* (Caryophyllaceae); *Matricaria chamomilla, Eupatorium ayapana* (Compositae); and other plants
64) Umbelliprenin	7-farnesyloxy	*Angelica archangelica* (Umbelliferae)
65) Ostruthin	7-hydroxy-6-geranyl	*Peucedanum ostruthium* (Umbelliferae)
66) Osthenol	7-hydroxy-8-isopentenyl	*Angelica archangelica* (Umbelliferae)

TABLE 4 (*continued*)

Compound	Substituents	Sources
67) Osthol	7-methoxy-8-isopentenyl	*Peucedanum ostruthium* (Umbelliferae)
68) Auropten	7-methoxy-8-epoxyisopentenyl	*Citrus sinensis* (Rutaceae)
69*a*) Esculin	6,7-dihydroxy-6-glucoside	*Aesculus hippocastanum, A. Pavia* (Hippocastanaceae); *Gelsemium sempervirens* (Loganiaceae); *Brunfelsia hopeana* (Solanaceae); *Euphorbia lathyrus* (Euphorbiaceae); and other plants
69*b*) Cichoriin	6,7-dihydroxy-7-glucoside	Flowers of *Cichorium intybus* (Compositae)
70*a*) Fabiatrin	6-methoxy-7-hydroxy-7-primeveroside	Branches of *Fabiana imbricata* (Solanaceae)
70*b*) Scopolin	6-methoxy-7-hydroxy-7-glucoside	*Scopolia japonica, S. carniolica, S. lurida, Atropa belladonna, Mandragora autumnalis* (Solanaceae); *Convolvulus scammonia, Ipomoea purga* (Convolvulaceae); *Gelsemium sempervivens* (Loganiaceae); *Artemisia afra* (Compositae); *Murraya exotica* (Rutaceae)
71) Ayapin	6,7-methylenedioxy	*Eupatorium ayapana* (Compositae)
72) Daphnin	7,8-dihydroxy-7-glucoside	*Daphne mezereum, D. odora, D. gnidum, D. laureola, D. alpina, Arthrosolen polycephalus* (Thymelaeaceae); *Setaria italica* (Gramineae)
73) Limettin	5,7-dimethoxy	*Citrus limetta, C. limonum, C. medica* (Rutaceae)

TABLE 4 (*continued*)

Compound	Substituents	Sources
74) 7-Methoxy-5-geranyloxy-coumarin	7-methoxy-5-geranyloxy	West Indian lime oil *Luvunga scandens*, Rutaceae)
75) Toddalolactone	5,7-dimethoxy-6-(2,3-dihydroxyisopentyl)	Root bark of *Toddalia aculeata* (Rutaceae)
76) Ammoresinol	4,7-dihydroxy-3-farnesyl	*Dorema ammoniacum* (Umbelliferae)
77) Fraxin	6-methoxy-7,8-dihydroxy-8-glucoside	*Fraxinus excelsior, F. ornus, F. americana* (Oleaceae); *Aesculus Pavia, A. hippocastanum* (Hippocastanaceae); *Diervilla japonica, D. lonicera* (Caprifoliaceae)
78) Fraxinol	5,7-dimethoxy-6-glucoside	*Fraxinus excelsior* (Oleaceae)
79) Fraxidin	6,7-dimethoxy-8-hydroxy-8-glucoside	*Fraxinus excelsior*
80) Isofraxidin	6,8-dimethoxy-7-hydroxy-7-glucoside	*Fraxinus excelsior*
Furocoumarins:		
81) Psoralene (Ficusin)	.....	*Psoralea corylifolia* (Leguminosae); leaves of *Ficus carica* (Moraceae)
82) Peucedanin	2′-isopropyl-3′-methoxy	*Peucedanum officinale, Prangos pabularia* (Umbelliferae)

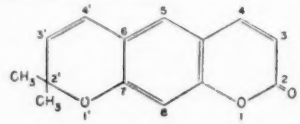
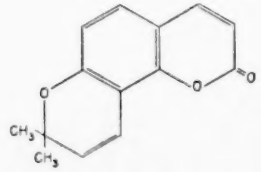
TABLE 4 (*continued*)

Compound	Substituents	Sources
83) Bergaptol	5-hydroxy	Bergamot oil from *Citrus bergamia* (Rutaceae)
84) Bergaptene (Heraclin)	5-methoxy	Bergamot oil from *Citrus bergamia, Fagara xanthoxyloides, Skimmia laureola* (Rutaceae); *Seseli indicum, Heracleum Sphondylium, Ligusticum acutilobum* (Umbelliferae); *Ficus carica* (Moraceae)
85) Bergamotin	5-geranyloxy	Bergamot oil (Rutaceae)
86) Isoimperatorin	5-isopentenyloxy	*Peucedanum ostruthium* (Umbelliferae)
87) Ostruthol	5-OCH_2—CH(OCOC(CH_3)=CH—CH_3)—$C(CH_3)_2OH$	*Peucedanum ostruthium*
88) Oxypeucedanin	5-epoxyisopentenyloxy	*Peucedanum ostruthium, P. officinale, Prangos pabularia* (Umbelliferae)
89) Imperatorin	8-isopentenyloxy	*Imperatoria ostruthium, Angelica glabra, A. archangelica* (Umbelliferae); *Aegle marmelos* (Rutaceae)
90) Xanthotoxol	8-hydroxy	Seeds and root of *Angelica archangelica* (Umbelliferae)
91) Xanthotoxin	8-methoxy	*Fagara xanthoxyloides, Ruta chalepensis, Luvunga scandens* (Rutaceae)
92) Isopimpinellin	5,8-dimethoxy	*Pimpinella saxifraga, Heracleum sphondylium, Seseli indicum* (Umbelliferae); West Indian lime oil, (*Luvunga scandens*, Rutaceae)

TABLE 4 (*continued*)

Compound	Substituents	Sources
93) Byak-angelicol	5-methoxy-8-epoxyisopentenyloxy	Constituent of Japanese drug (byakusi) from the root of *Angelica glabra* (Umbelliferae)
94) Byak-angelicin	5-methoxy-8-(2,3-dihydroxyisopentyloxy) (or 5-(2,3-dihydroxyisopentyloxy)-8-methoxy)	Root of *Angelica glabra* (Umbelliferae)
95) Phellopterin	5-methoxy-8-isopentenyloxy	*Angelica glabra, Phellopterus littoralis* (Umbelliferae)
96*a*) Nodakenin	2′,3′-dihydro-2′-(1-glucosoxyisopropyl)	*Peucedanum decursivum* (Umbelliferae)
96*b*) Marmesin	(optical isomer of the aglucone of nodakenin, nodakenetin)	*Aegle marmelos* (Rutaceae)
97) Angelicin	.....	Root of *Angelica archangelica* (Umbelliferae); seeds of *Psoralea corylifolia* (Leguminosae)
98) Isobergaptene	5-methoxy	Root of *Heracleum sphondylium, Pimpinella saxifraga* (Umbelliferae)

TABLE 4 (*continued*)

Compound	Substituents	Sources
99) Sphondin	6-methoxy	Root of *Heracleum sphondylium* (Umbelliferae)
100) Pimpinellin	5,6-dimethoxy	Root of *Pimpinella saxifraga* and *Heracleum sphondylium* (Umbelliferae)
101) Athamantin	2′,3′-dihydro-2′-(1-hydroxyisopropyl)-3′-hydroxy diisovaleryl ester	Root of *Peucedanum oreoselinum* (Umbelliferae)
Chromanocoumarins:		
102) Xanthyletin	.....	*Xanthoxylum americanum*, *Luvunga scandens* (Rutaceae)
103) Xanthoxyletin	5-methoxy	*Xanthoxylum americanum* (Rutaceae)
104) Luvangetin	8-methoxy	Root and fruit of *Luvunga scandens* (Rutaceae)
		
105) Seselin	.....	*Seseli indicum* (Umbelliferae); *Skimmia japonica* (Rutaceae)

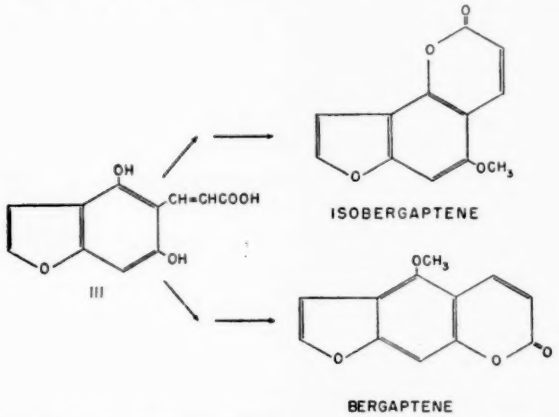
Coumarins based on 5,7-dihydroxycoumarin, or the phloroglucinol hydroxylation type, are especially characteristic of the Rutaceae where they are frequently accompanied by umbelliferone derivatives. The α,α-dimethylchromanocoumarins, xanthyletin (102) and xanthoxyletin (103), which are related to umbelliferone and 5,7-dihydroxycoumarin, respectively, and differ from each other only in the 5-methoxyl group possessed by the latter, have been isolated from *Xanthoxylum americanum.* The fruit rinds of *Citrus limetta* and several other *Citrus* species contain 5,7-dimethoxycoumarin, or limettin (73), while in orange-peel oil (*C. sinensis*) is found auropten (68), the epoxide of osthol. A compound closely related to limettin, 7-methoxy-5-geranyloxycoumarin (74), has been isolated from West Indian lime oil. Bergaptol (83), the 5-hydroxy-linear-furocoumarin having the phloroglucinol orientation, and its methyl and geranyl ethers, bergaptene (84) and bergamotin (85), have been found in the essential oil of *Citrus bergamia.* (Three bergaptol ethers of the isopentenyl type—isoimperatorin (86); its epoxide, oxypeucedanin (88); and ostruthol (87)—are also found in *Peucedanum ostruthium* of the Umbelliferae.) Another rutaceous species, *Luvunga scandens,* produces a series of related dimethylchromano- and furocoumarins. Although the degree of hydroxylation varies in this group of compounds, the coumarins found—xanthyletin (102), luvangetin (104), xanthotoxin (91) and isopimpinellin (92)—are based on the consistent pattern represented by the progressively more hydroxylated resorcinol, pyrogallol, and 1,2,3,5-tetrahydroxybenzene nuclei. All of the compounds, furthermore, have the linear arrangement of the furano- or chromano-ring with the pyrone ring. The alkyl substituents thus occupy the same relative positions in the various coumarins of the series.

Coumarins of the 6,7-dihydroxy type are of frequent occurrence in the Solanaceae, Compositae and Loganiaceae. Esculin (69*a*), fabiatrin (70*a*), scopolin (70*b*), cichoriin (69*b*), and ayapin (71) are examples of this type.

Fraxidin (79), isofraxidin (80) and fraxin (77) have identical structures except for the positions of methylation and glycosylation; i.e., all three are derivatives of 6,7,8-trihydroxycoumarin. These coumarins have been isolated from the bark of the ash tree (*Fraxinus excelsior,* Oleaceae) along with a fourth coumarin,

fraxinol (78), which, however, is a dimethyl ether of 5,6,7-trihydroxycoumarin.

Frequently a pair of isomeric coumarins appear to be derived from the same precursor when cyclization of the intermediate can take place in different directions. In most cases where this is possible, both isomers are found in the same source. The monomethoxyfurocoumarins, bergaptene (84) and isobergaptene (98), are coexistent in the umbelliferous herb, *Heracleum sphondylium*. These are clearly related to a precursor such as β-(2,6-dihydroxyfuro-(2′,3′-3,4)-phenyl)-acrylic acid (III) which by lactonization with the 2- or the 6-hydroxyl group, followed by methylation of the residual free hydroxyl, could produce either of the isomers.



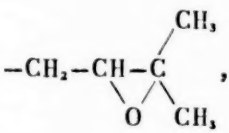
The isomeric dimethoxyfurocoumarins, pimpinellin (100) and isopimpinellin (92), which are also isolated from *H. sphondylium*, as well as from *Pimpinella saxifraga*, are related in the same way to β-(2,5,6-trihydroxyfuro-(2′,3′-3,4)-phenyl)-acrylic acid.

An interesting example of specificity of hydroxylation occurs in the genus *Angelica*. Whereas the coumarins in *Angelica archangelica* are based on a resorcinol- or pyrogallol-type nucleus (cf. angelicin (97), osthenol (66), umbelliprenin (64), imperatorin (89) and xanthotoxol (90)), *Angelica glabra*, from which the Japanese drug, byakusi, is obtained, contains a series of closely-related furocoumarins derived from the 1,2,3,5-tetra-hydroxybenzene nucleus. Included are phellopterin (95), byak-angelicin (94)

and byak-angelicol (93) which differ only in the oxidation state of the isopentenyl-type ether group. Imperatorin (89), whose formula is like that of phellopterin except that it lacks the 5-methoxyl substituent of the latter (i.e., it is constructed on a pyrogallol nucleus), is also found in *Angelica glabra.*

The wide variety of alkyl side-chains encountered among the natural coumarins show certain structural similarities which inspire speculation concerning their origins and biosynthetic relationships. The isopentenyl, or prenyl (as it is termed by Späth (1938)), moiety is the fundamental unit upon which most of these side-chains are based. The prenyl group exists as such in osthenol (66) and osthol (67), where it is attached directly to the benzene nucleus, and in imperatorin (89), isoimperatorin (86) and phellopterin (95), where it exists in an ether-linkage with the coumarin. The aromatic nucleus of the chromone peucenin (158) from *Peucedanum ostruthium,* the umbelliferous species which has provided so many coumarin derivatives, is also substituted with an isopentenyl group. Geranyl and farnesyl side-chains consisting of two or three prenyl groups linked together are found in several coumarins.

Modifications of the isopentenyl moiety, in which the double bond is oxidized, are also common. The epoxide,



is the variation found in auropten (68), byak-angelicol (93) and oxypeucedanin (88). In toddalolactone (75) and ostruthol (87) two hydroxyl groups replace the double bond forming the corresponding glycol, and in the latter compound the secondary hydroxyl group is esterified with α-methylcrotonic acid. This acid also is constructed on the isoprene or prenyl skeleton, an observation which constitutes further evidence for the prevalence of precursors and processes for the synthesis of this structural feature in the plant. Still another modification of the prenyl moiety, a 3-hydroxyisopentanyl group, occurs in the flavonol, icariin (208).

α,α-Dimethylpyran and isopropenylfuran rings are also obviously related to the prenyl skeleton. They are found in other classes of

compounds as well as the coumarin series (Table 5). The insecticide, rotenone (113), has a 2-isopropenyldihydrofuran ring, and several related rotenoids, including deguelin (109), tephrosin (110), toxicarol (111) and lonchocarpine (106), possess the dimethylpyran structure. The latter is also found in rottlerin (108) from the euphorbiaceous species, *Mallotus philippinensis,* and in evodione (107), a constituent of *Evodia elleryana* of the Rutaceae. Osajin (293) and pomiferin (294), two isoflavones, contain not only a dimethylpyran ring, but also an uncyclized prenyl group. The origin and interrelationships of these heterocyclic rings will be discussed later.

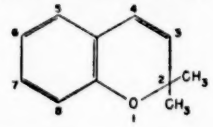
COMPOUNDS OF THE C_6-CLASS

The C_6-class of naturally-occurring benzenoid compounds, i.e., those with no aliphatic side-chain, is necessarily limited to phenols and their methyl and glycosidic ethers (Table 6). Although such substances as phloroglucinol, pyrogallol, catechol and resorcinol are isolated repeatedly in the degradation of natural products, since the basic nuclei of these aromatic hydroxy compounds are frequently encountered as a structural feature of naturally-occurring substances, their existence in the free state is limited to a few isolated instances or is unknown altogether. Phenol (114) itself is said to occur in the trunk, needles and cones of *Pinus sylvestris.* Catechol (117) is present in a species of *Ephedra* and in the pigmented, but not the colorless, scales of onions. There is some evidence for the presence of guaiacol (118) in the high-boiling fraction of celery-seed oil, and veratrole (119) has been observed in the seeds of *Sabadilla officinalis.* The existence of veratric acid (144) in the same plant material suggests a possible derivation of the ether by decarboxylation of the acid.

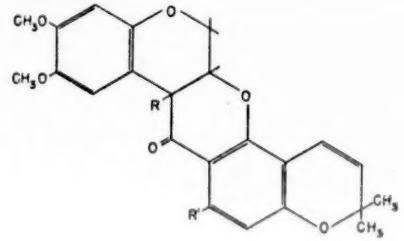
Hydroquinone (115) is found chiefly in pear leaves (*Pyrus communis*) and in various Ericaceae, principally arbutus and cranberry, where it is associated with its derivatives, arbutin (115*a*), a monoglycoside, and methylarbutin (116), the glycoside of hydroquinone monomethyl ether.

3,4,5-Trimethoxyphenol, or antiarol (120), possessing a hydroxylation pattern which, like those of resorcinol, catechol, phloroglucinol and pyrogallol, is a nucleus upon which many natural substances are based, is a constituent of the thickened milky juice of *Antiaris toxicaria* which has been used as an arrow poison.

TABLE 5. SOME NATURALLY-OCCURRING COMPOUNDS WITH α,α-DIMETHYLPYRAN AND ISOPROPENYLFURAN RINGS



Compound	Substituents	Sources
106) Lonchocarpine	5-hydroxy-6-benzyloxy	Seeds and roots of *Lonchocarpus sericens* (Leguminosae)
107) Evodione	5,7,8-trimethoxy-6-acetyl	*Evodia elleryana* (Rutaceae)
108) Rottlerin	5,7-dihydroxy-6-(2,4,6-trihydroxy-3-methyl-5-acetyl-benzyl)-8-cinnamoyl	Fruit glands of *Mallotus philippinensis* (Euphorbiaceae)



109) Deguelin	(R=R′=H)	*Derris elliptica, Tephrosia toxicaria, T. Vogelii* (Leguminosae)

TABLE 5 (*continued*)

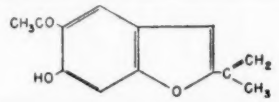
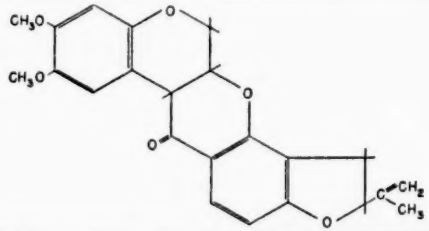
Compound	Substituents	Sources
110) Tephrosin	(R = OH; R′ = H)	*Derris, Tephrosia*
111) Toxicarol	(R = H; R′ = OH)	*Derris, Tephrosia*
112) Euparin		*Eupatorium purpureum* (Compositae)
113) Rotenone		*Derris, Lonchocarpus* (Leguminosae)

TABLE 6. NATURALLY-OCCURRING PHENOLS OF THE C_6-C_6-C_1- AND C_6-C_7-CLASSES

Compound	Substituents	Sources
114) Phenol	hydroxybenzene	Trunk, needles and cones of *Pinus sylvestris* (Pinaceae)
115) Hydroquinone	1,4-dihydroxybenzene	Leaves and flowers of *Vaccinium Vitis-idaea* (Ericaceae); leaf-buds of *Pyrus communis* (Rosaceae); *Protea mellifera* (Proteaceae); and other plants
115a) Arbutin	1,4-dihydroxybenzene-1-glucoside	*Pyrus communis* (Rosaceae); *Arctostaphylus Uva-ursi* and many other Ericaceae
116) Methyl-arbutin	1-hydroxy-4-methoxybenzene-1-glucoside	*Pyrus communis* (Rosaceae); *Illicium verum* (Magnoliaceae)
117) Pyrocatechol	1,2-dihydroxybenzene	*Ephedra monostachya* (Gnetaceae); pigmented onion scales (Liliaceae); and possibly other plants
118) Guaiacol	1-hydroxy-2-methoxybenzene	Possibly in the high-boiling fraction of celery-seed oil (*Apium graveolens*, Umbelliferae); *Guaiacum officinale* (Zygophyllaceae)
119) Veratrol	1,2-dimethoxybenzene	Seeds of *Sabadilla officinalis* (Liliaceae)
120) Antiarol	1,2,3-trimethoxy-5-hydroxybenzene	*Antiaris toxicaria* (Moraceae)
121) *p*-Cresol	1-methyl-4-hydroxybenzene	Small amounts in various oils from *Acacia farnesiana* (Leguminosae); *Gnaphalium arenarium* (Compositae); and other plants
122) *p*-Cresol methyl ether	1-methyl-4-methoxybenzene	Ylang-ylang oil (*Cananga odorata*, Anonaceae)
123) Creosol	1-methyl-3-methoxy-4-hydroxybenzene	Ylang-ylang oil
124) *m*-Phlorol	1-ethyl-3-hydroxybenzene	Root of *Arnica montana* (Compositae)

COMPOUNDS OF THE C_6-C_1- AND C_6-C_2-CLASSES

Many compounds of the C_6-C_1- and C_6-C_2-classes (Tables 6, 7 and 8), especially the benzaldehyde and benzoic acid derivatives, which are the most numerous types, may be regarded as degradation products of members of the C_6-C_3-class.

The relationship is particularly obvious between the various substituted benzaldehydes and the α-propenylbenzenes from which they could be derived by oxidative cleavage. Most of the typical arrangements of hydroxyl, methoxyl and methylenedioxy groups found in the naturally-occurring propenylbenzenes are also known among the natural benzaldehydes. *p*-Hydroxybenzaldehyde (132), anisaldehyde (133), vanillin (134) and piperonal (135) are so abundantly and widely distributed that they seem almost ubiquitous. Asaraldehyde (137), 2,4,5-trimethoxybenzaldehyde, is of rare occurrence. Its existence, therefore, in the same plant (*Asarum europaeum*) as the similarly-substituted propenylbenzene, asarone (18), is significant.

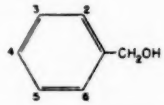
Salicylaldehyde (130) and *p*-methoxysalicylaldehyde (136) are fairly widespread benzaldehyde derivatives. Since *o*-hydroxyl groups are unknown among the propenyl benzenes, except where they occur in those polyhydroxylated derivatives typical of the Umbelliferae, degradation of coumarins or of coumarin precursors may be responsible for their formation. Such a proposal is also supported by the fact that coumarin, umbelliferone (in which the hydroxyl is *para* to the side-chain) and derivatives of umbelliferone are also the most widespread compounds in their class.

Benzaldehyde itself, and its simple derivatives, are found in many plants bound with hydrogen cyanide and a sugar in a cyanohydrin glycoside such as amygdalin or dhurrin.

In addition to the benzoic acid derivatives, such as protocatechuic (143), veratric (144), piperonylic (145) and gallic acids (146), having the usual patterns of hydroxyl substitution, a number of derivatives of methyl salicylate are found in this group of compounds. Methyl salicylate (139) itself, accompanied by its xyloglucoside, gaultherin (139*a*), is a constituent of birch bark and the fruit and leaves of the ericaceous species, *Gaultheria procumbens*. The arabino glucoside of methylsalicylate, volutin (139*b*), occurs in *Viola cornuta*. The roots of *Primula officinalis* have provided two isomeric glycosides of methoxysalicylic acid methyl

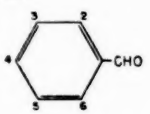
TABLE 7. NATURALLY-OCCURRING COMPOUNDS OF THE C_6-C_1-CLASS

Benzyl alcohol derivatives:



Compound	Substituents	Sources
125) Benzyl alcohol		Free or esterified with benzoic or cinnamic acid in *Hyacinthus orientalis* (Liliaceae); *Narcissus jonquilla, Polyanthes tuberosa* (Amaryllidaceae); *Dianthus caryophyllus* (Caryophyllaceae); *Eugenia caryophyllata* (Myrtaceae); and other plants
126*a*) Salicin	2-hydroxy-2-glucoside	Bark of willows and poplars (Salicaceae); flower buds of *Spiraea ulmaria* (Rosaceae)
126*b*) Populin	2-hydroxy-2-benzoylglucoside	Leaves and bark of *Populus tremula*, buds of *P. nigra, P. pyramidalis* (Salicaceae)
127) Anisalcohol	4-methoxy	*Vanilla planifolia* (Orchidaceae)
128) Salireposide	2,5-dihydroxy-[?]-benzoylglucoside	Leafy branches of *Salix repens* and *S. purpurea* (Salicaceae)

Benzaldehyde derivatives:



129) Benzaldehyde		Many plant sources, frequently as the cyanhydrin glycoside
130) Salicylaldehyde	2-hydroxy	Oil from *Spiraea ulmaria, S. digitata, S. lobata, S. filipendula* (Rosaceae); stem and root of *Cordia asperrima* (Boraginaceae); leaves of *Homalium tomentosum* (Flacourtiaceae); and other plants

TABLE 7 (*continued*)

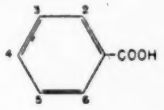
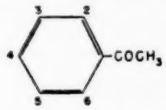
Compound	Substituents	Sources
131) Salinigrin	3-hydroxy-3-glucoside	*Salix discolor, S. nigra* (Salicaceae)
132) *p*-Hydroxybenzaldehyde	4-hydroxy	Resin from *Xanthorrhoea hastilis* and *X. australis* (Liliaceae); *Sorghum vulgare* (Gramineae)
133) Anisaldehyde	4-methoxy	*Illicium religiosum* (Magnoliaceae); *Acacia cavenia, A. farnesiana* (Leguminosae); *Protium carana* (Burseraceae); *Erica arborea* (Ericaceae); and other plants
134) Vanillin	3-methoxy-4-hydroxy	*Vanilla planifolia* (Orchidaceae); many other sources, often as a cleavage product
134*a*) Glucovanillin	4-glucoside of vanillin	Seed husks and roots of *Triticum repens* (Gramineae)
135) Piperonal	3,4-methylenedioxy	*Robinia pseudacacia* (Leguminosae); *Vanilla pompona* (Orchidaceae); *Spiraea ulmaria* (Rosaceae); and other plants
136) *p*-Methoxysalicylaldehyde	2-hydroxy-4-methoxy	Roots of *Chlorocodon Whiteii* (Asclepiadaceae)
137) Asaraldehyde	2,4,5-trimethoxy benzaldehyde	Essential oil from *Acorus calamus* (Araceae); *Asarum europaeum* (Aristolochiaceae)
Benzoic acid derivatives:		
		
138) Benzoic acid		Free or esterified with methanol, geraniol, benzyl alcohol, etc., in *Myroxylon Pereirae* (Leguminosae); *Cananga odorata* (Anonaceae); coto bark, *Cinnamomum* spp. (Lauraceae); and other plants
138*a*) Vacciniin	glucose 6-benzoate	*Vaccinum Vitis-idaea* (Ericaceae)

TABLE 7 (*continued*)

Compound	Substituents	Sources
139) Salicylic acid	2-hydroxy	As the methyl ester (methyl salicylate) in the leaves of *Gaultheria procumbens* (Ericaceae); the bark of *Betula lenta* (Betulaceae); and other plants
139*a*) Gaultherin	2-xyloglucoside of methyl salicylate	*Gaultheria procumbens* (Ericaceae); *Betula lenta* (Betulaceae); *Monotropa hypopitys* (Pyrolaceae)
139*b*) Violutin	arabinoglucoside of methyl salicylate	*Viola cornuta* (Violaceae)
140) *p*-Hydroxybenzoic acid	4-hydroxy	Pods of *Bignonia catalpa* (Bignoniaceae); *Grindelia robusta* (Compositae)
141) Primeverin	2-primeveroside of 2-hydroxy-4-methoxy (methyl ester)	Roots of *Primula officinalis* (Primulaceae)
142) Primulaverin	2-primeveroside of 2-hydroxy-5-methoxy (methyl ester)	Roots of *Primula officinalis*
143) Protocatechuic acid	3,4-dihydroxy	*Illicium religiosum, I. anisatum* (Magnoliaceae); *Vitis vinifera* (Vitaceae); *Hibiscus sabdariffa, Thespesia lampas* (Malvaceae); pigmented onion skins (Liliaceae); and other plants
144) Veratric acid	3,4-dimethoxy	Seed of *Sabadilla officinalis* (Liliaceae); *Aconitum ferox* (Ranunculaceae)
145) Piperonylic acid	3,4-methylenedioxy	Coto and paracoto bark (Lauraceae)
146) Gallic acid	3,4,5-trihydroxy	Free and as glycoside in a vast number of plants
147) Sparassol	2,4-dihydroxy-6-methyl	*Sparassis ramosa, Evernia prunastri* (Clavariaceae); *Rhododendron japonicum* (Ericaceae)

TABLE 8. NATURALLY-OCCURRING ACETOPHENONE DERIVATIVES



Compound	Substituents	Sources
148) Acetophenone	.....	*Cistus ladaniferus, C. creticus* (Cistaceae); *Stirlingia latifolia* (Proteaceae)
149) *o*-Hydroxyacetophenone	2-hydroxy	*Chione glabra* (Rubiaceae)
150) Picein	4-hydroxy-4-glucoside	*Salix discolor* and other willows (Salicaceae); *Picea excelsa* (Pinaceae); *Amelanchier vulgaris* (Rosaceae)
151) Paeonol	2-hydroxy-4-methoxy	Root bark of *Paeonia Moutan* and other peonies (Ranunculaceae); *Xanthorrhoea tataena*, (Liliaceae); and other plants
152) Acetovanillone (Androsin, Apocynin)	3-methoxy-4-hydroxy	*Apocynum cannabimum, A. androsaemifolium* (Apocynaceae); *Buphane disticha* (Amaryllidaceae)
153) Phloroacetophenone	2,4,6-trihydroxy	*Xanthoxylum alatum, X. aubertia* (Rutaceae)
154) Phloroacetophenone dimethyl ether	2-hydroxy-4,6-dimethoxy	Essential oil of *Blumea balsamifera* (Compositae); numerous species of *Xanthoxylum* (Rutaceae)

ester; in primeverin (141) the methoxyl group is *para* to the ester function, while in primulaverin (142) it is *meta* to the ester group and *para* to the glycosylated hydroxyl group. The glycosidic residue, derived from the disaccharide, primeverose, is identical in the two compounds. Although its carbon skeleton, strictly speaking, is not that of a typical C_6-C_1-compound, sparassol (147), 2,4-dihydroxy-6-methylbenzoic acid methyl ester, is still another methyl salicylate derivative found in nature. The *ortho* methyl substituent as well as the hydroxylation pattern of sparassol suggest a relationship to the isocoumarins.

Benzoic acid (138) itself is of occasional occurrence, sometimes as the free acid, but often esterified with methanol, benzyl alcohol, geraniol or another alcohol. The acid and three of these esters have been isolated from ylang-ylang oil. Vacciniin (138*a*), the monobenzoate of D-glucose, is a constituent of cranberries.

Although the parent unsubstituted compound occurs elsewhere, the benzyl alcohol derivatives that occur in nature are found almost exclusively in the willow family. Salicin (126*a*), derived from willow and poplar bark, has a glucosidic hydroxyl *ortho* to the hydroxymethyl group. Populin (126*b*), which is found in several species of *Populus,* is identical except that one hydroxyl of the glucose residue is benzoylated. The structure of salireposide (128) is not completely established, but it is known to be a monobenzoylglucoside of 2,5-dihydroxybenzyl alcohol; the name is derived from its source in *Salix repens* as well as *S. purpurea.*

There are only a few C_6-C_1- and C_6-C_2-compounds in which the side-chain is found in the completely reduced state of a saturated aliphatic hydrocarbon, and they are formed only in small quantities in a very few plants (Table 6). The list includes *p*-cresol (121), *p*-cresol methyl ether (122), creosol (123) and the ethylbenzene derivative, *m*-phlorol (124).

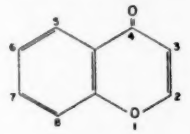
The small C_6-C_2-class of compounds also includes phenylethyl alcohol, a fragrant principle of rose oil, and several acetophenone derivatives (Table 8).

CHROMONES

The chromones other than 2-aryl so far found in nature are all 2-methyl derivatives (although in the case of chellol the methyl group bears a hydroxyl substituent, i.e., chellol is a 2-hydroxymethylchromone), and thus may be classified with the C_6-C_4-compounds. However, their hydroxylation patterns, substituent groups, and botanical distribution indicate their relationship to the coumarins. Only a few of these chromones are known, and they have been isolated from but three genera, two of which are umbelliferous (Table 9).

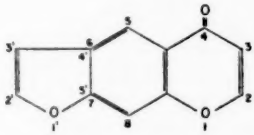
Eugenia aromatica and *E. caryophyllata* of the Myrtaceae have yielded three closely-related 2-methylchromones, all having the phloroglucinol nucleus. Eugenin (155) is 2-methyl-5-hydroxy-7-methoxychromone; eugenitin (156) and isoeugenitol (157) are,

TABLE 9. NATURALLY-OCCURRING CHROMONES



Compound	Substituents	Sources
155) Eugenin	2-methyl-5-hydroxy-7-methoxy	*Eugenia aromatica* (Myrtaceae)
156) Eugenitin	2,6-dimethyl-5-hydroxy-7-methoxy	*Eugenia caryophyllata*
157) Isoeugenitol	2,8-dimethyl-5,7-dihydroxy	*Eugenia caryophyllata*
158) Peucenin	2-methyl-5,7-dihydroxy-6-isopentenyl	*Peucedanum ostruthium* (Umbelliferae)

Furochromones:



159) Visnagin	2-methyl-5-methoxy	Fruit of *Ammi visnaga* (Umbelliferae)
160) Chellol glucoside	2-glucosoxymethyl-5-methoxy	Fruit of *Ammi visnaga*
161) Khellin	2-methyl-5,8-dimethoxy	Fruit of *Ammi visnaga*

respectively, 2,6-dimethyl-5-hydroxy-7-methoxy- and 5,7-dihydroxy-2,8-dimethylchromone. Since the latter two compounds were both isolated from *E. caryophyllata*, Schmid and Bolleter (1949) have suggested that 3-methyl-2,4-trihydroxybenzoylacetone is the common precursor. As in bergaptene and isobergaptene, the side-chain of this precursor can cyclize with either of the *ortho* hydroxyls, giving rise to two different compounds. The β-diketone, 2,4,6-trimethoxybenzoylacetone, named eugenone (163), has actually been found in *Eugenia*, and its unmethylated or partially methylated analog may be the precursor of eugenin. This is the only benzoylacetone that has been found in nature, but

TABLE 10. NATURALLY-OCCURRING C_6-COMPOUNDS WITH LONG ALIPHATIC SIDE-CHAINS

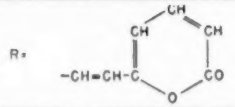
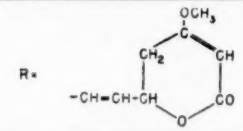
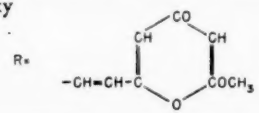
Compound	Substituents	Sources
162) Betuloside	4-hydroxy (R = glucoside of $—CH_2CH_2CHOHCH_3$)	*Betula alba* (Betulaceae)
163) Eugenone	2,4,6-trimethoxy (R = $COCH_2COCH_3$)	*Eugenia caryophyllata* (Myrtaceae)
164) Aspidinol	2,6-dihydroxy-4-methoxy-3-methyl (R = $COCH_2CH_2CH_3$)	Rhizomes of *Aspidium felix mas* and *A. spinulosum*, *Athyrium felix femina* (Polypodiaceae)
165) Zingerone	3-methoxy-4-hydroxy (R = $CH_2CH_2COCH_3$)	*Zingiber officinale* (Zingiberaceae)
166) Shogaol	3-methoxy-4-hydroxy (R = $CH_2CH_2COCH{=}CH(CH_2)_4CH_3$)	*Zingiber officinale*
167*a*) Piperic acid	3,4-methylenedioxy (R = $CH{=}CH{-}CH{=}CH{-}COOH$)	As amide of piperidine in *Piper nigrum*, *P. longum*, etc. (Piperaceae)
167*b*) Isochavicic acid	(Stereoisomer of piperic acid)	*Piper nigrum*
168) Phenylcoumalin		Coto bark (Lauraceae)
169) Paracotoin	3,4-methylenedioxy (R = same as for phenylcoumalin)	Paracoto bark (Lauraceae)

TABLE 10 (*continued*)

Compound	Substituents	Sources
170) Kawain		Rhizome and roots of *Piper methysticum* (Piperaceae)
171) Methysticin	3,4-methylenedioxy (R same as for kawain)	*Piper methysticum*
172) Yangonin	4-methoxy 	*Piper methysticum*
173) Ginkgolic acid	2-carboxy-3-hydroxy ($R=(CH_2)_7CH{=}CH(CH_2)_5CH_3$)	*Ginkgo biloba* (Ginkgoaceae)
174) Bilobol	3,5-dihydroxy ($R=(CH_2)_7CH{=}CH(CH_2)_5CH_3$)	*Ginkgo biloba*
175) Urushiol	2,3-dihydroxy ($R=(CH_2)_7CH{=}CH(CH_2)_5CH_3$)	*Rhus succedanea*, *R. ambigua*, *Semecarpus vernicifera*, etc. (Anacardiaceae); *Butea frondosa* (Leguminosae)
176) Pelandjanic acid (Pentaspadonic acid)	2-hydroxy-3-carboxy ($R=(CH_2)_7CH{=}CHCH_2CH{=}CH(CH_2)_4CH_3$)	*Pentaspadon Motleyi* (Anacardiaceae)

this is understandable in view of the lability of the β-diketone moiety: it is readily cleaved, and when an *ortho* hydroxyl group is available, cyclization to the chromone would be expected to be spontaneous.

The *o*-hydroxyacetophenone derivative, euparin (112), found in the composite, *Eupatorium purpureum,* is an example of another type of compound that may be or may arise from an intermediate in the biosynthesis (or degradation) of chromones. Most acetophenone derivatives found in nature, in fact, have a hydroxyl group *ortho* to the carbonyl substituent. These include not only the *o*-hydroxyacetophenones belonging to the simple C_6-C_2-group (Table 8), but also the chromans, evodione (107) and rottlerin (108).

Three structurally-similar furochromones, khellin (161), visnagin (159) and chellol glucoside (160), are found in the fruit of the umbelliferous herb, *Ammi visnaga.* All have the phloroglucinol hydroxylation pattern, though khellin bears an additional methoxyl group in the 8-position, making it a 1,2,3,5-tetrahydroxybenzene derivative. In all three also, the furan ring is in the linear arrangement with the chromone part of the molecule so that the carbon skeletons are identical. The characteristic 2-methyl group is modified in chellol glucoside by substitution with a hydroxyl group which is linked to a molecule of glucose. The chromone peucenin (158), from *Peucedanum ostruthium,* has a skeleton like that of visnagin except that the furan ring is represented by an isopentenyl group in the 6-position, adjacent to a 7-hydroxyl.

C_6-COMPOUNDS WITH LONG ALIPHATIC SIDE-CHAINS

In addition to eugenone, several other C_6-C_4-compounds in which the side-chain is not cyclized are known (Table 10). The observation that the side-chains among these compounds are oxidized only on the α- or γ-carbon atoms suggests the possibility of their derivation from a benzaldehyde derivative and acetone, or the biological equivalents of these substances. Piperic acid (167*a*), which is found as an amide of piperidine in the alkaloid piperin in several members of the Piperaceae, may originate from such an aldol condensation. In the resin from the root of *Piper methysticum* are three related C_6-C_7-compounds, kawain (170), methysticin (171) and yangonin (172), in which the last five carbons of

the 7-carbon side-chain are present as part of a lactone or chromone ring. The chemical and botanical relationships found in this group of compounds form the basis for suggestions regarding their biosynthesis which will be found in later sections of this review.

Phenylcoumalin (168) and the analogous compound, paracotoin (169), found in coto and paracoto bark, are also lactones of unsaturated acids. Although they are C_6-C_5-compounds and lack the vinyl bridge between the aromatic and lactone rings, their structure is fundamentally similar to that of kawain and methysticin. In both cases such features as hydroxylation on the carbon atoms in the β- and δ-positions to the carboxyl (or potential carboxyl) functions, and the presence of double bonds in conjugation with the carbonyl groups, suggest that aldol condensations are involved in the genesis of these compounds.

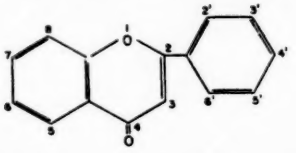
Another type of side-chain with more than three carbon atoms is that derived from fatty acids. Ginkgolic acid (173) and bilobol (174) from the maidenhair tree, *Ginkgo biloba,* are phenols bearing a 15-carbon unsaturated side-chain structurally related to palmitoleic acid. Urushiol (175), which has been isolated from several species of *Rhus* and other Anacardiaceae, and which apparently is responsible for the vesicant properties of these plants, is an isomer of bilobol and possesses the same fatty acid side-chain. The oily exudation of the wood of *Pentaspadon Motleyi* yields pentaspadonic, or pelandjanic, acid (176), another phenolic derivative with an alkyl substituent, in this case derived from linoleic acid.

FLAVONOID COMPOUNDS

The flavonoid compounds are characterized by their possession of a C_6-C_3-C_6 carbon skeleton consisting of two aromatic rings linked by an aliphatic three-carbon chain. Chiefly on the basis of the oxidation state of this aliphatic fragment the very large number of compounds included in the flavonoid classification is subdivided into such well-known types as anthocyanins, flavones, chalcones, etc. The basic structures of the various subgroups are shown in Tables 11 through 17.

Each of the two aromatic rings of flavonoid derivatives has certain characteristic types of hydroxylation patterns. The A-ring,

TABLE 11. NATURALLY-OCCURRING FLAVONES



Compound	Substituents	Sources
177) Flavone		Dust on leaves, stems and fruit-capsules of certain species of *Primula* (Primulaceae)
178) 5-Hydroxy-flavone	5-hydroxy	With flavone in the dust of *Primula imperialis* var. *gracilis* (Primulaceae)
179) Chrysin	5,7-dihydroxy	Buds of *Populus monilifera balsamifera, P. pyramidalis, P. nigris* (Salicaceae); heartwood of *Pinus strobus, P. cembra* (Pinaceae); *Oroxylum indicum* (Bignoniaceae)
179a) Toringin	7-glucoside of chrysin	Bark of *Pinus toringo* (Pinaceae)
180) Tecto-chrysin	5-hydroxy-7-methoxy	Buds of *Populus pyramidalis, P. nigra* (Salicaceae); heartwood of *Pinus strobus* (Pinaceae)
181) Primetin	5,8-dihydroxy	With flavone on the leaves of *Primula modesta* (Primulaceae)
182) Pratol	4′-methoxy-7-hydroxy	Flowers of *Trifolium pratense* and *T. incarnatum* (Leguminosae)
183) Baicalin	5,6,7-trihydroxy-7-glucuronic acid	*Scutellaria baicalensis, S. columnae* (Labiatae); *Oroxylum indicum* (Bignoniaceae)
184) Oroxylin-A	5,7-dihydroxy-6-methoxy	Root bark of *Oroxylum indicum* (Bignoniaceae)
185) Wogonin	5,7-dihydroxy-8-methoxy	*Scutellaria baicalensis* (Labiatae)

TABLE 11 (*continued*)

Compound	Substituents	Sources
186) Apigenin	4′,5,7-trihydroxy	Yellow *Dahlia* (Compositae); *Andropogon Sorghum* (Gramineae); and other plants
186*a*) Apiin	[?]-apioglucoside of apigenin	*Petroselinum sativum* (Umbelliferae)
186*b*) Cosmetin	7-glucoside of apigenin	Flowers of *Cosmos bipinnatus*, leaves and stems of *Euphorbia thymifolia* (Euphorbiaceae)
186*c*) Apigenin-5-glucoside	5-glucoside of apigenin	*Amorpha fruticosa* (Leguminosae)
187) Acacetin	4′-methoxy-5,7-dihydroxy	*Robinia pseudacacia* (Leguminosae)
187*a*) Acaciin	7-diglucoside of acacetin	*Robinia pseudacacia*
187*b*) Linarin	7-rutinoside of acacetin	*Linaria vulgaris* (Scrophulariaceae)
188) Buddleoflavonol	3-acetyl-4′-methoxy-5,7-dihydroxy	As the glycoside, buddleoflavonoloside, $C_{30}H_{34}O_{15}$, in flowers and leaves of *Buddleia variabilis* (Loganiaceae)
189) Genkwanin (Pudduметin)	4′,5-dihydroxy-7-methoxy	*Prunus puddum* (Rosaceae)
190) 5-Hydroxy-4′,7-dimethoxyflavone	5-hydroxy-4′,7-dimethoxy	Birch buds (Betulaceae)
191) Ginkgetin	5,8-dihydroxy-4′-methoxy*	Leaves of *Ginkgo biloba* (Ginkgoaceae)
192) Scutellarin	4′,5,6,7-tetrahydroxy-[?]-glucuronide	*Scutellaria altissima*, *S. indica*, etc.; *Galeopsis Tetrahit*; *Teucrium chamaedrys* (Labiatae)
193*a*) Pectolinarin	5,7-dihydroxy-4′,6-dimethoxy-7-rutinoside	Flowers of *Linaria vulgaris* (Scrophulariaceae)
193*b*) Neolinarin	5,7-dihydroxy-4′,6-dimethoxy-7-dirutinoside	Flowers of *Linaria vulgaris*

* 5,8-Dihydroxy-4′-methoxy flavone, which was the structure originally assigned to ginkgetin (Furukawa, 1932, 1933), was recently synthesized by Baker and Flemons (1948) and by Baker, Flemons and Winter (1949), and was found to have different properties from ginkgetin.

TABLE 11 (*continued*)

Compound	Substituents	Sources
194) Luteolin	3′,4′,5,7-tetrahydroxy	*Reseda luteola* (Resedaceae); *Genista tinctoria* (Leguminosae); and other plants
194*a*) Galuteolin	5-glucoside of luteolin	Seeds of *Galega officinalis* (Leguminosae); stems of *Equisetum arvense* (Equisetaceae)
194*b*) Luteolin-7-glucoside	7-glucoside of luteolin	Leaves of *Digitalis purpurea* (Scrophulariaceae)
194*c*) Chaerophyllin	[?]-galactoside of luteolin	Flowers and seed capsules of *Chaerophyllum sylvestre* (Umbelliferae)
194*d*) Caesioside	[?]-primeveroside of luteolin	Leaves of *Salix caesia* (Salicaceae)
195) Fukugetin	3′,4′,5,7-tetrahydroxy-6-(epoxy-*p*-hydroxycinnamoyl)	Bark of *Garcinia spicata*, *Xanthocymus ovalifolia* (Guttiferae)
196) Chrysoeriol	4′,5,7-trihydroxy-3′-methoxy	*Eriodictyon glutinosum* (Hydrophyllaceae)
197*a*) Diosmin	3′,5,7-trihydroxy-4′-methoxy-7-rhamnoglucoside	*Hyssopus officinalis*, *Mentha crispa* (Labiatae); *Scrophularia nodosa*, *Linaria genistifolia* (Scrophulariaceae); *Toddalia aculeata* (Rutaceae); *Dahlia variabilis* (Compositae); and other plants
197*b*) Hydroxyapiin methyl ether	7-apioglucoside of diosmetin	*Petroselinum sativum* (Umbelliferae)
198) Lotusin	2′,4′,5,7-tetrahydroxy-7-maltose-cyanhydrin	Sap of *Lotus arabicus* (Leguminosae)
199) Ponkanetin	4′,5,6,7,8-pentamethoxy	*Citrus povensis* (Rutaceae)
200) Tricin	4′,5,7-trihydroxy-3′,5′-dimethoxy	*Triticum dicoccum* (Gramineae)
201) Nobiletin	3′,4′,5,6,7,8-hexamethoxy	*Citrus nobilis* (Rutaceae)
202) Acrammerin	3′,4′,5′,5,7-pentahydroxy-8-methoxy	Pods of *Gleditsia triacanthos* (Leguminosae)

TABLE 11 (*continued*)

Compound	Substituents	Sources
Flavonols (3-hydroxyflavones):		
203) Galangin	3,5,7-trihydroxy	Rhizome of *Alpinia officinarum* (Zingiberaceae)
204) Galangin monomethyl ether	3-methoxy-5,7-dihydroxy	Rhizome of *Alpinia officinarum*
205) Izalpinin	3,5-dihydroxy-7-methoxy	Seeds of *Alpinia chinensis*
206) Kaempferol	3,4′,5,7-tetrahydroxy	Occurs free and as glycoside in many plants
206*a*) Kaempferitrin (Trifolin, Afzein)	3-rhamnoside of kaempferol	Leaves of *Indigofera arrecta, Trifolium pratense, Afzelia* spp. (Leguminosae)
206*b*) Robinin	3-robinoside,7-rhamnoside of kaempferol	*Robinia pseudacacia* (Leguminosae)
206*c*) Kaempferol-3-rhamnoglucoside	3-rhamnoglucoside of kaempferol	*Calystegia japonica* (Convolvulaceae)
206*d*) Populnin	7-glucoside of kaempferol	*Thespesia populnea* and *Gossypium herbaceum* (Malvaceae)
206*e*) Equisetrin	7-diglucoside of kaempferol	*Equisetum arvense* (Equisetaceae)
206*f*) Kaempferin	[?]-diglucoside of kaempferol	*Cassia angustifolia* (Leguminosae)
206*g*) Lespedin	3,7-dirhamnoside of kaempferol	*Lespedeza cyrtobotrya* (Leguminosae)
207) Kaempferide	4′-methoxy-3,5,7-trihydroxy	*Alpinia officinarium* (Zingiberaceae)
208) Icariin	4′-methoxy-3,5,7-trihydroxy-8-(3-methyl-3-hydroxybutyl)-[?]-rhamnoside-[?]-glucoside	*Epimedium micranthum* (Berberidaceae)
209) Rhamnocitrin	3,4′,5-trihydroxy-7-methoxy	Fruits of *Rhamnus cathartica* (Rhamnaceae)
210) Datiscetin	2′,3,5,7-tetrahydroxy	As the rutinoside, datiscin, in *Datisca cannabina* (Datiscaceae); *Paeonia albiflora* var. *hortensis* (Ranunculaceae)

TABLE 11 (*continued*)

Compound	Substituents	Sources
211) Fisetin	3,3′,4′,7-tetrahydroxy	As the glycoside tannic acid (fustin tannide) in the wood of *Rhus cotinus*, *R. succedanea*, *Schinopsis Lorentzii* (Anacardiaceae); and other plants
212) Tangeretin	3,4′,5,6,7-pentamethoxy	Rind of *Citrus nobilis* var. *deliciosa* (Rutaceae)
213) Herbacitrin	3,4′,5,7,8-pentahydroxy-7-glucoside	*Gossypium indicum*, *G. herbaceum* (Malvaceae)
214) Tambuletin	3,4′,5,7-tetrahydroxy-8-methoxy	*Xanthoxylum acanthopodium* (Rutaceae)
215) Tambulin	3,5-dihydroxy-4′,7,8-trimethoxy	*Xanthoxylum acanthopodium*
216) Auranetin	3,4′,6,7,8-pentamethoxy	*Citrus aurantium* (Rutaceae)
217) Quercetin	3,3′,4′,5,7-pentahydroxy	Occurs free and as glycoside in many plants
217*a*) Isoquercitrin	3-glucoside of quercetin	*Zea Mays* (Gramineae); *Gossypium* spp. (Malvaceae); *Ambrosia artemisifolia* (Compositae); *Sapium sebiferum* (Euphorbiaceae); *Equisetum arvense* (Equisetaceae)
217*b*) Quercitrin	3-rhamnoside of quercetin	Many sources, including *Quercus tinctoria* (Fagaceae)
217*c*) Quercimeritrin	7-glucoside of quercetin	*Prunus emarginata*, *P. virginiana*, *P. serotina* (Rosaceae); *Gossypium hirsutum* (Malvaceae); *Helianthus annus* (Compositae)
217*d*) Hyperin	3-galactoside of quercetin	Grimes Golden, Stayman winesap and Jonathan apples (Rosaceae); *Hypericum perforatum* (Guttiferae); *Betula verrucosa* (Betulaceae)
217*e*) Rutin	3-rutinoside (or rhamnoglucoside) of quercetin	Many sources, including *Sophora japonica* (Leguminosae); *Ruta graveolens* (Rutaceae); *Eschscholtzia californica* (Papaveraceae)

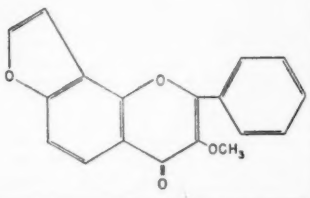
TABLE 11 (*continued*)

Compound	Substituents	Sources
217*f*) Meratin	3-diglucoside of quercetin	*Meratia praecox* (Calycanthaceae)
217*g*) Avicularin	3-arabinoside of quercetin	*Polygonum aviculare* var. *buxifolium* (Polygonaceae)
217*h*) Quercituron	[?]-glucuronide of quercitrin	Leaves of *Phaseolus vulgaris* (Leguminosae)
217*i*) Incarnatrin	[?]-glucoside of quercetin	*Trifolium incarnatum* (Leguminosae)
218) Isorhamnetin	3′-methoxy-3,4′,5,7-tetrahydroxy	*Typha angustata* (Typhaceae); *Caltha palustris, Delphinium zalil* (Ranunculaceae); *Cheiranthus Cheiri* (Cruciferae); *Cassia acutifolia, C. angustifolia, Trifolium pratense* (Leguminosae); *Ambrosia artemisifolia* (Compositae)
218*a*) Persicarin	3-potassium bisulfate ester of isorhamnetin	*Persicaria Hydropiper* (Polygonaceae)
218*b*) 3,4′-Diglucosidyl-isorhamnetin	3,4′-diglucoside of isorhamnetin	*Crocus* pollen (Iridaceae)
219) Garcinin	3,3′,4′,5,7-pentahydroxy-8-*p*-hydroxybenzyl	Bark of *Garcinia spicata* (Guttiferae)
220) Rhamnetin	3,3′,4′,5-tetrahydroxy-7-methoxy	
220*a*) Xanthorhamnin	3-trirhamnoside of rhamnetin	*Rhamnus infectorius, R. catharticus, R. Purshianus* (Rhamnaceae)
221) Rhamnazin	3′,7-dimethoxy-3,4′,5-trihydroxy	*Rhamnus infectorius* (Rhamnaceae); *Polygonum Hydropiper* (Polygonaceae)
222) Morin	2′,3,4′,5,7-pentahydroxy	*Chlorophora tinctoria, Maclura braziliensis, Artocarpus integrifolia* (Moraceae)
223) Robinetin	3,3′,4′,5′,7-pentahydroxy	Wood of *Robinia pseudacacia* and *Gleditsia monosperma* (Leguminosae)

TABLE 11 (*continued*)

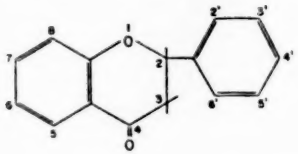
Compound	Substituents	Sources
224) Kanugin	3,3′,7-trimethoxy-4′,5′-methylenedioxy	*Pongamia glabra* (Leguminosae)
225) Thapsin (Calycopterin)	4′,5-dihydroxy-3,6,7,8-tetramethoxy	*Digitalis Thapsi* (Scrophulariaceae); leaves of *Calycopteris floribunda* (Combretaceae)
226) Quercetagetin	3,3′,4′,3,5,6,7-hexahydroxy	Flowers of *Tagetes patula* and *T. erecta* (Compositae)
226*a*) Quercetagitrin	7-glucoside of quercetagetin	*Tagetes erecta* (Compositae)
227) Patuletin	3,3′,4′,5,7-pentahydroxy-6-methoxy	Flowers of *Tagetes patula* (Compositae)
228) Gossypetin	3,3′,4′,5,7,8-hexahydroxy	*Gossypium herbaceum* (Malvaceae)
228*a*) Gossypitrin	7-glucoside of gossypetin	*Gossypium herbaceum*, *Hibiscus sabdariffa* (Malvaceae)
228*b*) Gossypin	8-glucoside of gossypetin	*Gossypium indicum*, *Hibiscus esculutus*, *H. irbifolium* (Malvaceae)
229) Ternatin	4′,5-dihydroxy-3,3′,7,8-tetramethoxy	*Melicope ternata* (Rutaceae)
230) Meliternin	3′,4′-methylenedioxy-3,5,7,8-tetramethoxy	*Melicope ternata*
231) Myricetin	3,3′4′,5′,5,7-hexahydroxy	Many sources including *Ilaematoxylon campechianum* (Leguminosae); *Pistachia terebinthus*, *Rhus coriaria* (Anacardiaceae); *Arctostaphylos Uva-ursi* (Ericaceae); *Ampelopsis meliaefolia* (Vitaceae)
231*a*) Myricitrin	3-rhamnoside of myricetin	*Myrica rubia*, *M. Gale* (Myricaceae); *Nymphaea alba* (Nymphaeaceae); *Calluna vulgaris* (Ericaceae); *Corylus avellana* (Betulaceae); *Cercis silignastrum* (Leguminosae)

TABLE 11 (*continued*)

Compound	Substituents	Sources
231*b*) Cannabiscitrin	3′-glucoside of myricetin	*Hibiscus cannabinus* (Malvaceae)
232) Erianthin	3,3′,4′,6,8-pentamethoxy-5,7-dihydroxy	Flowers of *Blumea erianthα* (Compositae)
233) Hibiscitrin	3,3′,4′,5,5′,7,8-heptahydroxy-3-glucoside	*Hibiscus sabdariffa, H. cannabinus* [?], (Malvaceae)
234) Gardenin	5-hydroxy-3,3′,4′,5′,6,8-hexamethoxy	Resinous secretion of *Gardenia lucida* (Rubiaceae)
235) Karanjin 		*Pongamia glabra* (Leguminosae)

which is the benzene nucleus fused to the heterocycle in most flavonoids, and which is the ring adjacent to the carbonyl group of the C_3-fragment in chalcones and dihydrochalcones, is typically substituted according to a phloroglucinol hydroxylation pattern. A remarkably large number of flavonoids have hydroxyl substituents in the *para* and the two *ortho* positions of the A-ring; this pattern is universal among the many anthocyanins and among the known dihydrochalcones and catechins, but there are a number of eceptions among the other groups. The most frequent variation is the absence of one of the *ortho* hydroxyls (the 5-substituent of the compounds having a pyrone ring). This condition prevails in five different chalcones, flavanones and benzalcoumaranones which have been isolated from *Coreopsis;* in fustin (254) and fisetin (211), a flavanonol and flavonol, respectively, occurring together in *Rhus* and *Schinopsis;* kanugin (224) and karanjin (235), flavonols isolated from *Pongamia glabra;* and in a few other flavonoids. A relatively large proportion of the isoflavones (C_6-C_3-C_6-compounds related to the flavones, but in which the benzene rings are attached to the first and second carbon atoms of the C_3-

TABLE 12. NATURALLY-OCCURRING FLAVANONES



Compound	Substituents	Sources
236) Dihydrochrysin	5,7-dihydroxy	Heartwood of *Pinus montana*, *P. banksiana* and *P. cembra* (Pinaceae)
237) Desmethoxymatteucinol	5,7-dihydroxy-6,8-dimethyl	*Matteuccia orientalis* (Polypodiaceae)
238) Alpinetin	5-hydroxy-7-methoxy (structure uncertain)	*Alpinia chinensis* (Zingiberaceae)
239) Liquiritin	4′,7-dihydroxy-4′-glucoside	*Glycyrrhiza glabra* var. *glandulifera* (Leguminosae)
240) Naringenin	4′,5,7-trihydroxy	
240*a*) Naringin	7-rhamnoglucoside of naringenin	Fruit of *Citrus decumana* (Rutaceae); *Nothofagus Dombeyi* (Fagaceae); *Prunus serotina* (Rosaceae)
240*b*) Salipurposide	5-glucoside of naringenin	Bark of *Salix purpurea* (Salicaceae)
241) Sakuranin	4′,5-dihydroxy-7-methoxy-5-glucoside	*Prunus yedoensis* and *P. serrulata* (Rosaceae)
242) Isosakuranetin	4′-methoxy-5,7-dihydroxy	Flowers of *Citrus trifoliata* (Rutaceae)
243) Matteucinol	4′-methoxy-5,7-dihydroxy-6,8-dimethyl	Leaves and stems of *Matteuccia orientalis* (Polypodiaceae)
244) Citronin	2′-methoxy-5,7-dihydroxy-7-rhamnoglucoside	*Citrus limon* (Rutaceae)
245) Isopedicin	6-hydroxy-5,7,8-trimethoxy	*Didymocarpus pedicellata* (Gesneriaceae)

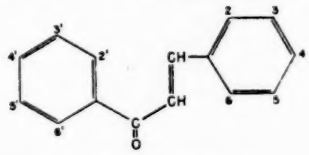
TABLE 12 (*continued*)

Compound	Substituents	Sources
246) Eriodictyol	3′,4′,5,7-tetrahydroxy	*Eriodictyon glutinosum, E. californicum* and *E. angustifolium* (Hydrophyllaceae)
247) Homoeriodictyol	3′-methoxy-4′,5,7-trihydroxy	*Eriodictyon glutinosum* (Hydrophyllaceae)
248) Hesperidin	4′-methoxy-3′,5,7-trihydroxy-7-rhamnoglucoside	Fruits of many species of *Citrus* (Rutaceae)
249) Butin	3′,4′,7-trihydroxy	Flowers of *Butea frondosa* (Leguminosae)
249*a*) Butrin	3′,7-diglucoside of butin	Flowers of *Butea frondosa*
250) 8-Methoxybutin	3′,4′,7-trihydroxy-8-methoxy	Flowers of *Coreopsis grandiflora* (Compositae)
Flavanonols (3-hydroxyflavanones):		
251) Alpinone	3,5-dihydroxy-7-methoxy-2-methyl	Seeds of *Alpinia japonica* (Zingiberaceae)
252) Pinobanksin	3,5,7-trihydroxy	Heartwood of *Pinus banksiana* and other species of *Pinus* (Pinaceae)
253) Katsuranin	3,4′,5,7-tetrahydroxy	*Cercidiphyllum japonicum* (Cercidiphyllaceae); *Nothofagus Dombeyi* (Fagaceae); *Prunus serotina* (Rosaceae)
254) Fustin	3,3′,4′,7-tetrahydroxy	Wood of *Rhus cotinus, R. succedanea, Schinopsis Lorentzii* (Anacardiaceae); and other plants
255) Taxifolin	3,3′,4′,5,7-pentahydroxy	Douglas-fir heartwood (*Pseudotsuga Douglasii*, Pinaceae)
256) Ampelopsin	3,3′,4′,5′,5,7-hexahydroxy	*Ampelopsis meliaefolia* (Vitaceae)

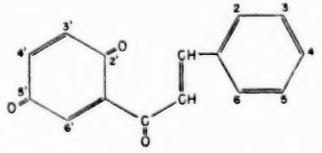
fragment, rather than to the first and third) also lack the 5-hydroxyl substituent.

The *para* hydroxyl group is missing on the A-ring of 5-hydroxyflavone (178) and the flavone, primetin (181), from certain species of *Primula*. The latter has the unusual 5,8-substitution pattern also thought to occur in the A-ring of the flavone, ginkgetin (191).

TABLE 13. NATURALLY-OCCURRING CHALCONES



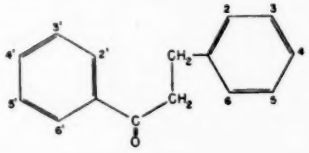
Compound	Substituents	Sources
257) Isosali-purposide	2′,4,4′,6′-tetrahydroxy-2-glucoside	Bark of *Salix purpurea* (Salicaceae)
258) Butein	2′,3,4,4′-tetrahydroxy	*Coreopsis Douglasii, C. gigantea, Cosmos sulfureus, Dahlia variabilis* (Compositae); *Butea frondosa* (Leguminosae)
259) Pedicin	2′,5′-dihydroxy-3′,4′,6′-trimethoxy	*Didymocarpus pedicellata* (Gesneriaceae)
260) Pedicellin	2′,3′,4′,5′,6′-pentamethoxy	*Didymocarpus pedicellata*
261*a*) Isocarthamin	2′,3′,4,4′,6-pentahydroxy-3′-glucoside	*Carthamus tinctorius* (Compositae)
261*b*) Carthamin	(quinoid-enol form of isocarthamin)	*Carthamus tinctorius*
262) Stillopsidin	2′,3,4,4′,5′-pentahydroxy	*Coreopsis Stillmanii* (Compositae)



263) Pedicinin	3′,6′-dihydroxy-4′-methoxy	*Didymocarpus pedicellata*
264) Methyl-pedicinin	3′,4′-dimethoxy-6′-hydroxy	*Didymocarpus pedicellata*

The flavonol, gardenin (234), the isoflavone, tatoin (280), and flavone (178) itself are the only other examples in which the hydroxyl group *para* to point of attachment of the C_3-fragment is lacking; the latter compound, which has no hydroxyl substituents on either the A-ring or the B-ring, except for the heterocyclic

TABLE 14. NATURALLY-OCCURRING DIHYDROCHALCONES

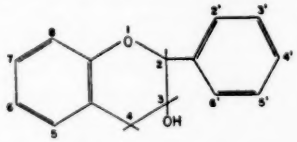


Compound	Substituents	Sources
265) Phloretin	2′,4,4′,6′-tetrahydroxy	
265*a*) Phloridzin	2′-glucoside of phloretin	Root bark of various rosaceous fruit trees; *Micromelum teprocarpum* (Rutaceae)
265*b*) Glycyphyllin	2′-rhamnoside of phloretin	*Smilax glycyphylla* (Liliaceae)
266) Asebotin	2′,4,6′-trihydroxy-4′-methoxy-2′-glucoside	*Andromeda japonica* (Ericaceae)

oxygen atom, occurs naturally as the dust on certain species of *Primula*.

Hydroxylation in the *meta* (6- and 8-) * positions of the A-ring (in addition to the *ortho* (5-) and *para* (7-) positions) is fairly frequent, particularly among the flavones and flavonols, but there

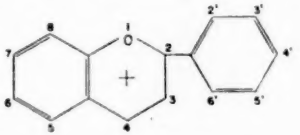
TABLE 15. NATURALLY-OCCURRING CATECHINS



Compound	Substituents	Sources
267) Catechin	3′,4′,5,7-tetrahydroxy	Various species of *Acacia* (Leguminosae); *Uncaria gambir* (Rubiaceae)
268) Arachidose	4′,5,7-trihydroxy-3′-methoxy	As a glucoside (arachidoside) in the skin of the seeds of *Arachis* spp. (Leguminosae)

* Flavone system of numbering; cf. (I), p. 79.

TABLE 16. NATURALLY-OCCURRING ANTHOCYANINS



Compound	Substituents	Sources
269) Pelargonidin	3,4′,5,7-tetrahydroxy	
269*a*) Callistephin	3-glucoside of pelargonidin	*Callistephus chinensis* (Compositae); *Dianthus caryophyllus* (Caryophyllaceae)
269*b*) Fragasin	3-galactoside of pelargonidin	*Fragara vesca* (Rosaceae)
269*c*) Pelargonin (Punicin)	3,5-diglucoside of pelargonidin	*Pelargonium zonale* (Geraniaceae); *Centaurea cyanus* (Compositae); *Pharbitis Nil* (Convolvulaceae); and other plants
269*d*) Monardein (Salvianin)	a derivative of pelargonin with malonic acid monomethyl ester and *p*-hydroxycinnamic acid	*Monarda didyma, Salvia coccinea, S. splendens* (Labiatae)
270) Cyanidin	3,3′,4′,5,7-pentahydroxy	
270*a*) Chrysanthemin (Asterin)	3-glucoside of cyanidin	*Chrysanthemum indicum, Callistephus chinensis* (Compositae); *Lycoris radiata* (Amaryllidaceae); red autumnal foliage of *Acer circumlobatum, A. ornatum* (Aceraceae)
270*b*) Idaein	3-galactoside of cyanidin	*Vaccinium Vitis-idaea, Vaccinium Myrtillus* (Ericaceae); skins of Jonathan and Stayman Winesap apples (Rosaceae); leaves of *Fagus sylvatica* (Fagaceae); *Fatsia japonica* (Araliaceae)
270*c*) Keracyanin (Oleocyanin)	3-rhamnoglucoside of cyanidin	*Prunus avium* (Rosaceae); ripe olives (Oleaceae)

TABLE 16 (*continued*)

Compound	Substituents	Sources
270*d*) Prunicyanin	probably a 3-bioside (rhamnose and a hexose) of cyanidin)	*Prunus spinosa* (Rosaceae)
270*e*) Antirrhinin	possibly a 3-bioside (rhamnose and glucose) of cyanidin	*Antirrhinum majus, Linaria vulgaris* (Scrophulariaceae); *Ribes sanguineum* (Saxifragaceae)
270*f*) Mecocyanin	3-gentiobioside of cyanidin	*Papaver Rhoeas* (Papaveraceae)
270*g*) Cyanin	3,5-diglucoside of cyanidin	*Rosa gallica* (Rosaceae); *Centaurea cyanis* (Compositae); and other plants
271) Peonidin	3,4′,5,7-tetrahydroxy-3′-methoxy	
271*a*) Oxycoccicyanin	3-glucoside of peonidin	*Oxycoccus macrocarpus* (=*Vaccinium macrocarpum*) *Vaccinium Vitis-idaea* (Ericaceae)
271*b*) Peonin	3,5-diglucoside of peonidin	*Paeonia arborea, P. albiflora* var. *hortensis* (Ranunculaceae); *Pharbitis Nil* (Convolvulaceae)
272) Delphinidin	3,3′,4′,5,5′,7-hexahydroxy	
272*a*) Violanin	3-*p*-hydroxycinnamoyl-rhamnoglucoside of delphinidin	*Viola tricolor* (Violaceae)
272*b*) Gentianin	[?]-*p*-hydroxy-cinnamoyl-3-glucoside of delphinidin	*Gentiana acaulis* (Gentianaceae)
272*c*) Nasunin	3-bioside of delphinidin	*Solanum melongena* var. *esculentum* (Solanaceae)
272*d*) Hibiscin (Hiviscin)	glycoside (glucose and an aldopentose) of delphinidin	*Hibiscus sabdariffa* (Malvaceae)
272*e*) Hyacin	diglucoside of delphinidin	*Hyacinthus orientalis* (Liliaceae)
272*f*) Delphin	3,5-diglucoside of delphinidin	*Delphinium* spp. (Ranunculaceae); *Salvia patens* (Labiatae); *Verbena hybrida* (Verbenaceae); and other plants

TABLE 16 (*continued*)

Compound	Substituents	Sources
272*g*) Delphinin	dibenzoyldiglycoside of delphinidin	*Delphinium consolida* (Ranunculaceae)
273) Petunidin	3,3′,4′,5,7-pentahydroxy-5′-methoxy	
273*a*) Petunin (Muscadinin?)	3,5-diglucoside of petunidin	*Petunia hybrida* (Solanaceae); Hunt muscadine grapes (Vitaceae)
274) Malvidin	3,4′,5,7-tetrahydroxy-3′,5′-dimethoxy	
274*a*) Oenin (Cyclamin, Ampelopsin)	3-glucoside of malvidin	Skins of black grapes (Vitaceae); *Cyclamen europaeum* (Primulaceae); *Ampelopsis quinquefolia* (Vitaceae)
274*b*) Primulin	3-galactoside of malvidin	
274*c*) Ensatin	[?]-*p*-hydroxycinnamoyl-3-bioside of malvidin	*Iris ensata* (Iridaceae)
274*d*) Malvin	3,5-diglucoside of malvidin	*Malva silvestris* (Malvaceae); *Primula viscosa*, *P. integrifolia* (Primulaceae)
274*e*) Negretein	[?]-*p*-hydroxycinnamoyl-[?]-glycoside (glucose + isorhodeose) of malvidin	Violet-colored potato (Solanaceae)
275) Hirsutidin	3,4′,5-trihydroxy-3′5′,7-trimethoxy	
275*a*) Hirsutin	3,5-diglucoside of hirsutidin,	*Primula hirsuta* (Primulaceae)
276) Peltogynidin	3,3′,4′,5,7-pentahydroxy-8-methyl	From the leucoanthocyanins of *Copaifera pubiflora* and *Peltogynum* species (Leguminosae)
277) 6-Hydroxycyanidin	3,3′,4′,5,6,7-hexahydroxy	As a glycoside in *Fagus sylvatica* (Fagaceae); *Prunus spinosa* (Rosaceae); *Taxus* spp. (Pinaceae)
278) Gesneridin	4′,5,7-trihydroxy	

TABLE 16 (*continued*)

Compound	Substituents	Sources
278*a*) Gesnerin	5-glucoside of gesneridin	*Gesnera fulgens* (Gesneriaceae)
278*b*) "4',5,7-Trigalloglucoxy-1-chlorobenzopyroxone"	4',5,7-trigallogluco-side of gesneridin (postulated structure, see footnote, p. 138)	*Chiranthodendron pentadactylon* blossoms
279) 3',5'-dimethoxygesnerin	5-glucoside of 4',5,7-trihydroxy-3',5'-dimethoxy	*Gesnera fulgens*

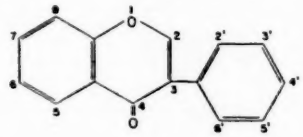
are very few examples of substitution in a *meta* position among the compounds which lack the usual *ortho* or *para* hydroxyls. In other words, hydroxylation in the 6- and 8-positions, when it occurs, is usually in addition to the 5,7-hydroxylation.

The other benzene ring of flavonoid compounds, termed the B-ring, is characteristically substituted in the same manner as the aromatic ring of the typical C_6-C_3-compounds, or is completely unsubstituted. The B-rings of all but six of the many known naturally-occurring flavonoid and isoflavonoid compounds are either unsubstituted, or substituted with one, two or three hydroxyl functions in the *para* (4'-), *para* and one *meta* (3',4'-), or *para* and both *meta* (3',4',5'-) positions, respectively. The exceptions are all compounds which have a hydroxyl group in the *ortho* (2'-) position of the B-ring; they include the flavanone, citronin (244); the flavone, lotusin (198); the flavonols, datiscetin (210) and morin (222); and two isoflavones from soya bean, isogenistin (287) and methylisogenistin (288). Lotoflavin and morin have an additional hydroxyl group in the *para* position.

In general, the four most frequently-encountered B-ring substitution patterns occur with about equal frequency among the various groups of flavonoids; however, anthocyanins in which the B-ring is an unsubstituted phenyl group are conspicuously absent, and only ampelopsin (256) among the chalcones and flavones has three hydroxyl groups on the B-ring.

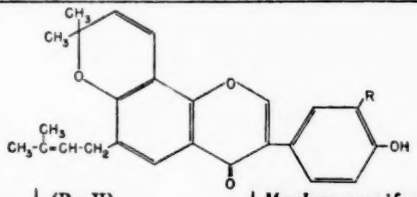
Relatively very few flavonoid compounds have alkyl substituents of the sort so typical of coumarins and chromones. The hydroxyisopentenyl group of icariin (208) has already been mentioned

TABLE 17. NATURALLY-OCCURRING ISOFLAVONES



Compound	Substituents	Sources
280) Tatoin	4′,5-dihydroxy-8-methyl	*Soja hispida* (Leguminosae)
281) Daidzin	4′,7-dihydroxy-7-glucoside	Soya-bean meal (*Soja hispida*)
282) Ononin	4′-methoxy-7-hydroxy-7-glucoside	*Ononis spinosa* (Leguminosae)
283*a*) Genistin	4′,5,7-trihydroxy-7-glucoside	*Soja hispida, Genista tinctoria* (Leguminosae)
283*b*) Sophoricoside	4′,5,7-trihydroxy-4′-glucoside	*Sophora japonica* (Leguminosae)
283*c*) Sophorabioside	4′,5,7-trihydroxy-4′-rhamnoglucoside	*Sophora japonica*
284) Methylgenistein	4′,5,7-trihydroxy-8-methyl	*Soja hispida*
285) Biochanin-A	4′-methoxy-5,7-dihydroxy	*Chana* germ
286) Prunitrin	4′,5-dihydroxy-7-methoxy-[?]-glucoside	Bark of *Prunus emarginata* (Rosaceae)
287) Isogenistin	2′,5,7-trihydroxy-[?]-glucoside	*Soja hispida* (Leguminosae)
288) Methylisogenistin	2′,5,7-trihydroxy-8-methyl-[?]-glucoside (possible structure)	*Soja hispida*
289) Pseudobaptisin	3′,4′-methylenedioxy-7-hydroxy-7-rhamnoside	Root of *Baptisia tinctoria* (=*Sophora tinctoria* (Leguminosae)
290) Tectoridin	6-methoxy-4′,5,7-trihydroxy-7-glucoside	Rhizomes of *Iris tectorum* and *Belamcanda chinensis* (Iridaceae)
291) Santal	3′,4′,5-trihydroxy-7-methoxy (probable structure)	*Santalum album* (Santalaceae); *Baphia nitida* (Leguminosae)

TABLE 17 (*continued*)

Compound	Substituents	Sources
292) Iridin	3′,5,7-trihydroxy-4′,5′,6-trimethoxy-7-glucoside	Rhizomes of *Iris germanica, I. pallida* and *I. florentina* (Iridaceae)
		
293) Osajin	(R=H)	*Maclura pomifera* (Moraceae)
294) Pomiferin	(R=OH)	*Maclura pomifera*

(p. 104); karanjin (235), another flavonol, has a furan ring fused to the A-ring in the 7,8-position. Several other C_6-C_3-C_6 compounds have alkyl or acyl substituents of different types. The flavone, fukugetin (195), has a *p*-hydroxyepoxycinnamoyl substituent in the 6-position; the same plant source, *Garcinia spicata*, also yields the flavonol, garcinin (219), which is alkylated with a *p*-hydroxybenzyl group in the 8-position. Buddleo-flavonol (188), which is actually a flavone, has an acetyl group attached at the 3-position. Several flavonoids have methyl substituents on the A-ring. The closely-related flavanones from *Matteucia orientalis*, matteucinol (243) and desmethoxymatteucinol (237), are 6,8-dimethyl derivatives; and three isoflavones from soya bean—tatoin (280), methylgenistein (284) and methylisogenistin (288)—each have a methyl group in the 8-position. The flavanonol, alpinone (251), also has a methyl substituent; however, its attachment at the 2-position (that is, on the end carbon of the C_3-fragment, rather than on an aromatic ring) makes this a unique and interesting case. Alpinone thus possesses not only the basic 2-phenylchromone structure of the usual flavonoid compound, but also the 2-methylchromone skeleton typical of other naturally-occurring chromones (cf. khellin (161), peucenin (158), etc.).

Among the anthocyanins it is not uncommon for one or more of the anthocyanidin or sugar hydroxyls to be esterified with an organic acid such as *p*-hydroxybenzoic, malonic, *p*-hydroxycinnamic,

or 3,5-dimethoxy-4-hydroxycinnamic acid. Monardein (*169a*), gentianin (*272b*) and ensatin (*274c*) are typical of these acylated anthocyanins.

Among some classes of flavonoid compounds methylation and glycosylation is restricted to hydroxyl groups in certain specific positions in the molecule, or at least occurs with much greater frequency in some positions than in others. Sugar residues in the anthocyanin series, for example, have been found at the 3- and 5-positions only *. If the anthocyanin has only one sugar residue, it is always linked to the 3-hydroxyl †; a second sugar molecule may be attached to a hydroxyl of the first sugar, giving a 3-bioside, or to the 5-position of the pigment molecule, giving a 3,5-dimonoside. Flavonols are also most commonly glycosylated in the 3-position, though several members of this group have sugar substituents in other locations—the 7-position most frequently, but also the 3′- and 4′-positions, and even the 8-position (in gossypin (*228b*)). Flavones and isoflavones which have no 3-hydroxyl are usually 7-glycosides; in a very few flavones the sugar residue is attached to the 5-hydroxyl group. The sugar is usually linked to one of the *ortho* hydroxyls of the A-ring in the known chalcone and dihydrochalcone glycosides; however, the few members of this class that have been isolated may not be representative in this respect. In general, glycosylation is infrequent on the B-ring, and particularly rare on the 4′-hydroxyl; no known anthocyanins have been shown to possess a sugar in the 4′-position. The flavanone, liquiritin (239), the isoflavone, sophoricoside (*283b*), and a 3,4′-diglucoside of the flavonol, isorhamnetin (*218b*), apparently are the only flavonoid compounds in which a 4′-sugar substituent has been established with certainty.

The tendency for methoxylation to occur to a greater extent in some positions than in others is not so great as in the case of glycosylation. Hydroxyl groups in the 6- and 8-positions of flavones

* The structure reported by Pallares and Garza (1949) for the anthocyanin isolated from macpalxochitl blossoms (*Chiranthodendron pentadactylon*) has sugar substituents in the 4′-, 5-, and 7-positions. The experimental evidence, however, does not preclude a structure in which one, or perhaps even two, of the sugar residues are linked to a hydroxyl group of another sugar molecule, forming a biose or triose residue, rather than to hydroxyls of the anthocyanidin.

† In the exceptional case of the anthocyanins, gesnerin (*278a*) and 3′,5′-dimethoxygesnerin (*279*), which lack a 3-hydroxyl, the single sugar residue is attached to the 5-hydroxyl.

and flavonols are as apt to be found methylated as those in the 3-,5-, or 7-positions, and even 4′-methoxylation is sometimes encountered. This is not true of the anthocyanins, however; in this series the 4′-hydroxyl is always free. Hirsutin (*275a*) is the only anthocyanin in which either of the hydroxyl groups of the A-ring is methoxylated. In general, therefore, methoxyl groups in the anthocyanins are found only in the 4′- and 5′-positions. Among the chalcones and flavones, methoxyl groups are relatively infrequent except for the compounds derived from *Didymocarpus pedicellata.* One further observation in connection with methoxylation of flavonoid compounds is of interest. This is the striking tendency for complete methylation of all of the hydroxyl substituents in the flavones and flavonols isolated from various species of *Citrus.* Each of the four compounds, nobiletin (201), ponkanetin (199), tangeretin (212) and auranetin (216), has five or six methoxyl substituents and no free hydroxyl groups.

As in other classes of natural products, there are many examples in the flavonoid series, of related compounds occurring together in the same plant or family of plants. These can be found by referring to the tables, and many of them will be discussed later in this review. A few typical cases, however, are listed below:

The root of *Alpinia officinarum* of the Zingiberaceae contains the four flavonols, galangin (203), galangin monomethyl ether (204), kaempferide (207) and izalpinin (205), in addition to the flavanonol, alpinone (251). Each of these compounds is hydroxylated or methoxylated in the 3-, 5-, and 7-positions.

The four chalcones from *Didymocarpus pedicellata* (259, 260, 263, 264), and the flavanone, isopedicin (245), from the same source, all have a completely hydroxylated A-ring and an unsubstituted B-ring.

The two flavonols from *Tagetes patula* and *T. erecta,* quercetagetin (226) and patuletin (227), are identically substituted except that the 6-hydroxyl group of the former is replaced by a methoxyl group in the latter.

The basic hydroxylation patterns of ternatin (229) and meliternin (230), flavonols from *Melicope ternata,* also are identical.

The flavonols of two malvaceous genera exhibit a rather intricate relationship. Herbacitrin (213) and gossypetin (228) have been obtained from *Gossypium,* while myricetin (231) and hibiscitrin (233), as well as gossypetin, are found in *Hibiscus.* Herbacitrin,

gossypetin and hibiscitrin have identical 5,7,8-trihydroxylated A-rings, and the 3′,4′,5′-trihydroxysubstituted B-rings of myricetin and hibiscitrin are also identical.

The co-occurrence of such related compounds in a particular species or genus suggests a genetic basis for their structural similarities. It would appear in these cases that a common precursor having a characteristic, genetically-determined (presumably) substitution pattern may be modified subsequently along several different paths giving rise to compounds which have certain distinctive structural features in common.

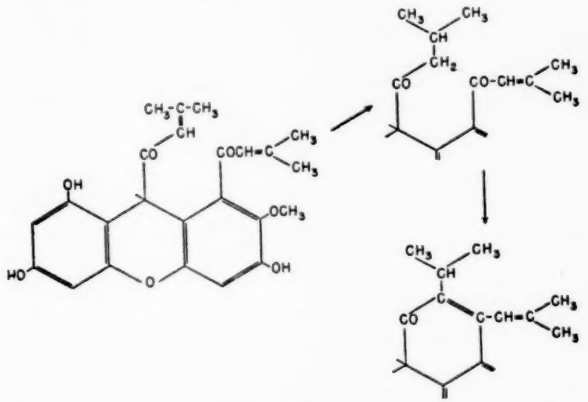
BENZOPHENONE, XANTHONE AND STILBENE DERIVATIVES

In addition to the flavonoid compounds there are several other groups of non-nitrogenous natural products with two benzenoid rings. These may be linked, as in the benzophenone and xanthone derivatives, with a single carbon atom, or by a two-carbon bridge, as in the stilbenes. The aromatic nuclei in brazilin (XLIX) and hematoxylin (L) are joined by a more complicated fused-ring system based on a branched-chain carbon skeleton.

Most of the known benzophenone derivatives (Table 18) have been found in the bark and wood of a few species of the laurel and mulberry families. Almost invariably one ring is of the phloroglucinol, or A-ring type, the other unsubstituted or a 3,4-dihydroxy derivative of the typical B-ring substitution pattern. The sole exception is *p*-hydroxybenzophenone (295) which was recently isolated from the leaves of *Talauma mexicana*.

The basic skeleton of the xanthones (Table 19) is obviously closely related to that of the benzophenones. Naturally-occurring xanthone derivatives are rare, but the few that are known also reflect this relationship in the positions of their substituent hydroxyl groups. If the heterocyclic oxygen atom is regarded as a hydroxyl substituent, as in the case of the flavonoid compounds (see footnote, p. 84), then the xanthones too are seen to have one aromatic ring of the phloroglucinol type (except for euxanthone (302) and ravenelin (306), which appear to have lost the *para* substituent of their A-type rings), and one ring of the B-type. Ravenelin has several exceptional features, including a methyl substituent and an unusual arrangement of hydroxyl substituents; it is, however, a mold metabolite, and not a product of higher plants.

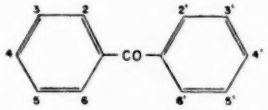
Although mangostin (307), strictly speaking, is not a xanthone, it clearly belongs with this class of compounds. It appears to be derived from a xanthone to which isopentenoyl side-chains have become attached in the 4- and 5-positions; the additional six-membered ring would presumably result from an aldol condensation between these substituents after reduction of the double bond of the 5-isopentenoyl group.



The known naturally-occurring stilbene derivatives (Table 20) vary only slightly with respect to their hydroxylation patterns. The most striking feature of this group of compounds is the universal occurrence of the unusual 3,5-dihydroxylation pattern on one of the two aromatic rings. The substitution patterns of the second ring are of the C_6(B)-type. Unsubstituted and *p*-hydroxy substituted phenyl rings are most numerous; rhapontin (314), however, is one of the few naturally-occurring compounds which has a 3-hydroxy-4-methoxy phenyl group, while the unusual 2′,4′-dihydroxyphenyl nucleus is found in two stilbenes—hydroxyresveratrol (313) and chlorophorin (315). The latter compound, it is interesting to note, is derived from the same genus as morin, 2′,3,4′,5,7-pentahydroxy flavone (222).

Like mangostin in the xanthone series, the stilbene, chlorophorin, has an isoprenoid side-chain. This is attached in the *para* position on the 3,5-dihydroxy-substituted ring, and appears to have the structure, $—CH_2CH=C(CH_3)CH_2CH=CHCH(CH_3)_2$, though

TABLE 18. NATURALLY-OCCURRING BENZOPHENONE DERIVATIVES



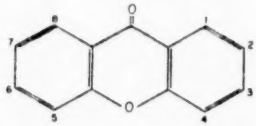
Compound	Substituents	Sources
295) *p*-Hydroxybenzophenone	4-hydroxy	Leaves of *Talauma mexicana* (Magnoliaceae)
296) Cotoin	2,6-dihydroxy-4-methoxy	Coto bark (Lauraceae)
297) Hydrocotoin	2,4-dimethoxy-6-hydroxy	Coto bark
298) Methylhydrocotoin	2,4,6-trimethoxy	Paracoto bark (Lauraceae)
299) Maclurin	2,3′,4,4′,6-pentahydroxy	Wood of *Morus tinctoria* (=*Maclura aurantiaca*) (Moraceae)
300) Protocotoin	2,4-dimethoxy-6-hydroxy-3′,4′-methylenedioxy	Coto bark
301) Methylprotocotoin (Hydroxyleucotin)	2,4,6-trimethoxy-3′,4′-methylenedioxy	Coto bark

the position of the second double bond is uncertain. At any rate, it is obviously composed of two prenyl units, and is a further example of the wide distribution of this five-carbon skeleton.

SUMMARY

From the foregoing it seems apparent that the aromatic rings and the aliphatic side-chains of numerous groups of naturally-occurring substances are related, on the basis of certain characteristic structural features, to the various fragments of the $C_6(A)$-C_3-$C_6(B)$ flavonoid skeleton. The A-ring, the benzene nucleus which in most flavonoids is fused to the heterocyclic moiety, is typified by a phloroglucinol or, less commonly, a resorcinol hydroxylation pattern, though additional hydroxylation up to complete substitution of the ring is possible. A-type rings are also found in other groups of compounds which possess two aromatic

TABLE 19. NATURALLY-OCCURRING XANTHONES



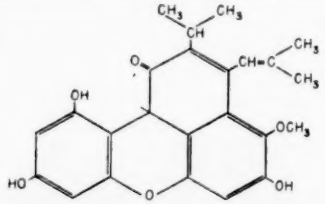
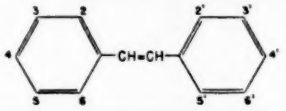
Compound	Substituents	Sources
302) Euxanthone	1,7-dihydroxy	*Mangifera indica* (Anacardiaceae); heartwood of *Platonia insignis* (Guttiferae)
303) Gentisin	1,7-dihydroxy-3-methoxy	Root of *Gentiana lutea, Swertia japonica* (Gentianaceae)
304) Desmethylswertianol	1,3,5,8-tetrahydroxy	*Swertia tosaensis* (Gentianaceae)
305) Swertianolin	1,3,8-trihydroxy-5-methoxy-1-glucoside	*Swertia tosaensis*
306) Ravenelin	1,4,8-trihydroxy-3-methyl	Metabolite of the fungi *Helminthosporium ravenelii, H. turcicum*
307) Mangostin		Fruit skins of *Garcinia mangostana* (Guttiferae)

TABLE 20. NATURALLY-OCCURRING STILBENES



Compound	Substituents	Sources
308) Pinosylvin	3,5-dihydroxy	Heartwood of *Pinus sylvestris*, *P. nigra* (Pinaceae)
309) Pinosylvin monomethyl ether	3-hydroxy-5-methoxy	Heartwood of *Pinus strobus*, *P. cembra*, *P. montana* (Pinaceae)
310) Pinosylvin dimethyl ether	3,5-dimethoxy	*Pinus nigra*, *P. palustris* (Pinaceae)
311) Resveratrol	3,4′,5-trihydroxy	Root of *Veratrum grandiflorum* (Liliaceae)
312) Pterostilbene	3,5-dimethoxy-4′-hydroxy	Red sandalwood (*Pterocarpus santalinus*, Leguminosae)
313) Hydroxy-resveratrol	2′,3,4′,5-tetrahydroxy	Root of *Veratrum grandiflorum* (Liliaceae)
314) Rhapontin	3,3′,5-trihydroxy-4′-methoxy-5-glucoside	Root of *Rheum emodi* (Polygonaceae)
315) Chlorophorin	2′,3,4′,5-tetrahydroxy-4-(3,7-dimethylocta-2,5-dienyl) (probable structure)	*Chlorophora excelsa* (Moraceae)

nuclei (xanthones, benzophenones), but only rarely, if at all, is the phenyl group of a naturally-occurring C_6-C_n-compound (where C_n is an aliphatic side-chain one, two, three, or more carbon atoms in length) substituted according to a phloroglucinol pattern. The C_6(B)-ring, which is the aryl group attached to the 2-position of the chromone or chroman moiety in most flavonoid substances, is typically a phenyl, 4-hydroxyphenyl, 3,4-dihydroxyphenyl, or 3,4,5-trihydroxyphenyl group. The 3- and 5-hydroxyl groups are frequently methylated, but the 4-hydroxyl is nearly always free. Rings with B-type hydroxylation patterns are extremely widespread among natural products occurring almost universally, as we have seen, among all sorts of C_6-C_n-compounds as well as in flavo-

noids, benzophenones, stilbenes, etc. The most distinctive feature of the C_3-moiety of the flavonoid skeleton is the variability in the extent and nature of the oxidation states it exhibits. Such variation occurs not only among the C_6-C_3-C_6-compounds where it constitutes the principal basis for subdivision of the flavonoid type compounds, but also among the C_6-C_3-derivatives (cf. coumarins, cinnamyl alcohol derivatives, propenylbenzenes, lignanes, etc.).

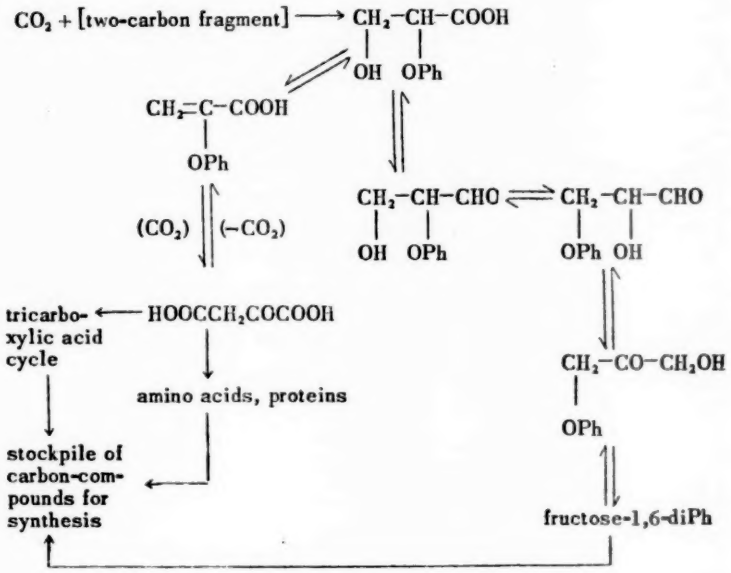
The Starting Materials for Synthesis

It is axiomatic that the metabolic processes of the plant are intimately bound up with the synthesis of cellular constituents. The ultimate source of carbon is the photosynthetically fixed carbon dioxide which is first introduced (Calvin, 1949) in the form of the low-molecular-weight compounds which are a part of the metabolic cycles involved in carbohydrate and amino acid metabolism. The introduction of carbon dioxide by the β-carboxylation of keto acids is another route by which carbon may be fixed in the cell (Part II), but this clearly rests upon the availability of carbon compounds formed in other ways. The ways in which further transformations of the carbon compounds prepared in this manner can take place are numerous, and it must be emphasized at the outset that the schemes which have so far been proposed to account for plant syntheses can be evaluated critically only on the basis of the kinds of processes and the kinds of substances known to occur in the cell.

The widespread occurrence in higher plants of the acids of the tricarboxylic acid cycle; the effects of pyruvic, citric, cis-aconitic, malic, succinic, isocitric and fumaric acids in promoting the growth and respiration of seedlings, excised roots and leaves; and the dominant role played by the amino acids, asparagine and glutamine, in the nitrogen metabolism of plants, are too well known to require extended comment (Bennet-Clark, 1949; Vickery, 1941). The reciprocal relationship between starch and the organic acids in crassulacean plants (Bonner and Bonner, 1948) shows that, at least in plants of this kind, the organic acids are not static constituents of the tissue but are directly involved in synthetic processes. Low-molecular-weight alcohols, aldehydes, ketones and acids occur widely in the higher plants (Rabinowitch, 1935). Besides the common and ubiquitous malic, succinic, oxalic and

citric acids, the important metabolic intermediates α-ketoglutaric, pyruvic and oxaloacetic acids have also been reported in green plants (Virtanen et al., 1939, 1943).

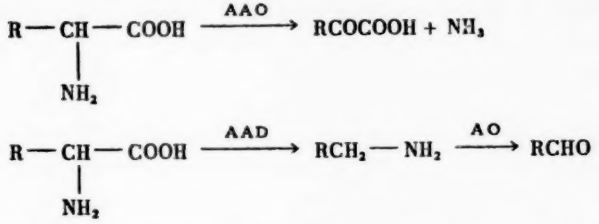
The relationship between photosynthesis and cellular metabolism can be represented in the following abbreviated form (Calvin, 1949):



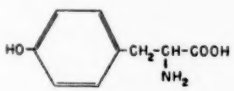
This scheme shows, although not in detail, the origin of the bulk of the fundamental building blocks of plant synthesis, in particular those to which need not be ascribed an origin unique to higher plants.

THE AMINO ACIDS

The place of amino acids in plant metabolism is an important one, and these substances can serve as a cellular source of α-keto acids and aldehydes through the action of amino acid oxidase (AAO), amino acid decarboxylase (AAD) (Schales and Schales, 1946) and amine oxidase (AO) (Werle and Pechman, 1949), the action of which may be represented in the following general way:

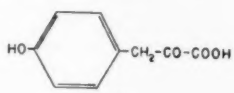


Tyrosine (IV) appears to have a special significance for two reasons: it is the putative precursor for the synthesis of numerous alkaloids, particularly those of the benzylisoquinoline group, and as such plays a prominent role in the existing theories of alkaloid biogenesis; and it is a representative of the important and widely-occurring C_6-C_3-group of compounds.

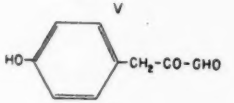


IV

As such it occupies a position of special significance, since its existence supports the inference that the related compounds *p*-hydroxyphenylpyruvic acid (V) and *p*-hydroxyphenylpyruvic aldehyde (VI) are available in the cell.



V

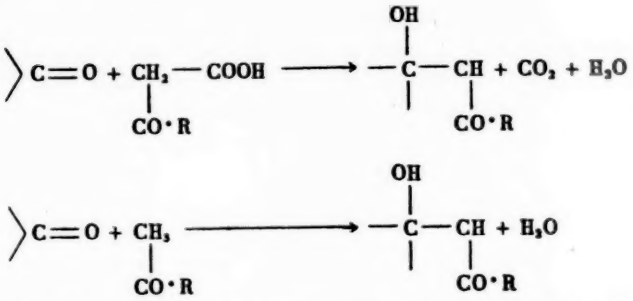


VI

Further discussion of these compounds, their possible roles in synthesis, and their relationship to the far more prevalent 3,4-dihydroxyphenyl analogues (Mothes and Pietz, 1937) and to compounds with side-chains of differing oxidation states will be reserved for a later section.

β-KETO ACIDS

The theories of alkaloid biogenesis of Schöpf and others (Winterstein and Trier, 1931; Schöpf and Thierfelder, 1935; Henry, 1949) emphasize the importance of assuming the presence of β-keto acids as cellular reactants. The unusual reactivity of the methylene group of a β-keto acid as compared with that of a methyl ketone (which is structurally equivalent to it, as the following equations show),

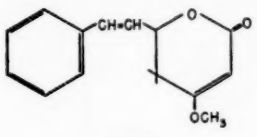


suggests that β-keto acids could serve as important building-blocks via aldol condensations of the kind which could occur without the mediation of specific enzymes. The experimental demonstration of the existence of these highly unstable compounds in plants has not been accomplished; but if they are formed in metabolic processes it would be expected not only that their isolation would be difficult or impossible, but because of their peculiar reactivity they would be unlikely to accumulate in isolable quantities. Secondary evidence of their existence can, however, be adduced. Numerous methyl ketones of the general structure $RCOCH_3$ are found in plants. These could arise by the decarboxylation of a β-keto acid:

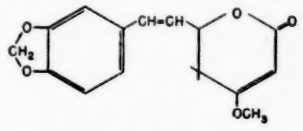
$$R \cdot CO \cdot CH_2 \cdot COOH \longrightarrow R \cdot CO \cdot CH_3 + CO_2$$

The ability of other kinds of organisms to produce methyl ketones is well known (Stärkle, 1924; Karrer and Haab, 1948; Thaler and Stählin, 1949*a*, *b*). Numerous *Penicillium* species are able to convert saturated, α,β-unsaturated and β-hydroxy fatty acids to methyl ketones, and contain an enzyme system capable of decarboxylating β-keto acids, converting them into methyl ketones.

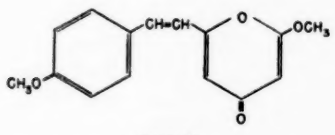
This is hardly proof of the existence of β-keto acids in plants, since the methyl ketones found in them could arise in other ways; but such a course is highly probable. Other evidence is found in the existence of substances in which the β-keto acid structure survives in a modified, stable form. Among such compounds are kawain, methysticin and yangonin:



kawain

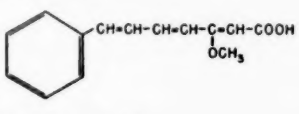


methysticin

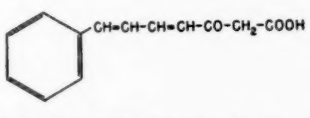


yangonin

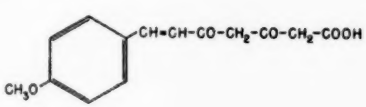
The first two of these are ethers of the enolic forms of β-keto acids, present as lactones. Kawain, for example, is converted by treatment with alkali into kawaic acid



the enol ether of the β-keto acid



Yangonin is of special interest because it is a modified β,δ-diketo acid; that is, it is related through simple hydrolytic changes to the following compound:



HEXOSES AND CYCLITOLS

Compounds which may serve as immediate progenitors of the six-carbon moieties of the C_6-C_3-C_6-compounds are, first, the hexoses, and, second, the cyclitols (inositol and related compounds). D-Glucose and D-fructose are the most ubiquitous of the hexoses, glucose being of almost universal occurrence either as the free sugar, in glucosides of many kinds, or in reserve carbohydrates such as starch and cellulose. The occurrence of D-fructose in analogous reserve polysaccharides (fructosans) is, while not so common, also worth mention. The equivalence of glucose, fructose and their polysaccharides through the medium of well-known enzymatic reactions, and the close relationship (Stumpf, 1948) of glucose and fructose to the trioses, glyceraldehyde and dihydroxyacetone (as phosphate esters), makes suspect any hypothetical direct relationship between a six-carbon non-sugar and a specific hexose. For this reason, the growth of a living organism or tissue fragment with a single, pure sugar as the only source of carbon, is not unequivocal evidence for the role of that sugar as the immediate precursor of the six-carbon substances which the organism may produce. In certain cases, however, a logical speculation may prescribe certain structural requirements for a reaction which may make compulsory the selection of a particular hexose as a reactant.

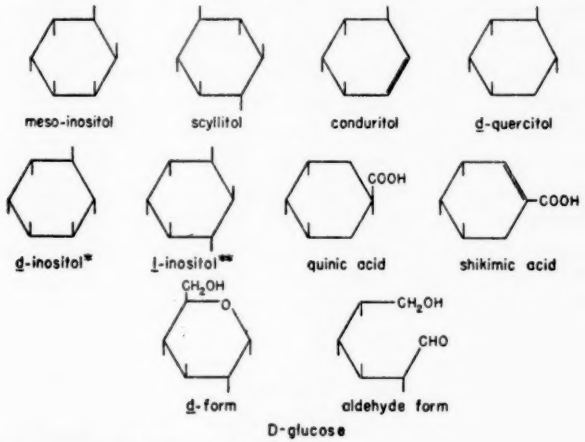
A case in point is represented by the important class of plant substances known as the inositols (Fletcher, 1948). Meso-inositol and several of its methyl ethers are found in plants; and in the form of phytin, the calcium-magnesium salt of its hexaphosphoric acid ester, meso-inositol is of wide occurrence. Other inositols (but not all of the theoretically possible hexahydroxycyclohexanes) as well as certain other polyhydroxycyclohexane derivatives also occur in plants (e.g., quercitol, conduritol).

The cyclitols are of special significance because of their structural relationship to D-glucose, to which the more common of the natural inositols are configurationally related, and to shikimic and quinic acids. The latter compounds appear to represent a link between the hexoses and the aromatic compounds (Fischer and Dangschat, 1935; Dangschat and Fischer, 1938). Inositol has been said to represent this link between the carbohydrates and the aromatic substances found in plants, but, as will be argued in the

sequel, it is more satisfactory to consider the inositols as products derived from a hypothetical precursor which is itself the true link to the aromatic compounds.

In Table 21 are shown some of the naturally-occurring cyclitols, with D-glucose in the cyclic (Haworth representation) and aldehyde forms for comparison.

TABLE 21. NATURALLY-OCCURRING CYCLITOLS



* As a monomethyl ether, quebrachitol.
** As a monomethyl ether, pinitol.

NOTE: Except where another group is shown, the vertical lines represent the positions of hydroxyl groups.

Three of the carbon atoms of most (but not all) of the naturally-occurring cyclitols have configurations which are the same as those of the 3,4,5-positions of glucose (and fructose). There has been much speculation (Fischer, 1944–5) regarding the biogenetic relationship of the cyclitols with D-glucose. The question of the position occupied by the cyclitols (in particular meso-inositol) in the scheme of biosynthesis of carbocyclic substances from hexoses is clearly related to the same problem, but there is no evidence at the present time to relate the cyclitols to each other or to other carbocyclic substances occurring in plants.

The hypothetical derivation of meso-inositol from D-glucose by means of a reaction which is formally of the aldol condensation

type, is discussed elsewhere in this review (p. 156). It has been pointed out there that the cyclization of 6-nitro-6-desoxy-D-glucose can hardly be called an imitation of a natural process, although the ingenious suggestion of Fischer, that, in the plant, phosphorylation of the 6-hydroxyl group of glucose furnishes the necessary activation of the methylene group for ring-closure, narrows the gap in the analogy.

When one considers the multiplicity of substances which occur in plants, and the chemical interrelationships between many of them, it is clear that it is often difficult to draw a clear line between the end-products and the raw materials of cellular synthesis. The problem is further complicated by the fact that an end-product formed in a reversible step from a reactive precursor, while not on the synthetic main line, may be available for synthetic purposes after reversal of the last step in its formation. For the purposes of the present review, however, it will be necessary to establish an arbitrary distinction between compounds thus related, and to consider relatively complex compounds as synthetic starting materials only if they appear to undergo modification without first reverting to precursors.

The Synthetic Mechanisms of the Living Cell

In the following discussion of the cellular reactions in which simple organic molecules are elaborated into more complex structures, it will be assumed at the outset that the processes in question are directly or indirectly under the control of enzymes: directly, when the enzyme must be present as a part of the system undergoing the reaction; indirectly, when molecules with sufficient reactivity to react in the absence of a participating enzyme are produced by a preliminary enzyme-mediated step (Schöpf, 1923). Evidence from the field of chemical genetics indicates, furthermore, that these processes are under particular genetic control. Genetic studies on higher plants, dealing especially with flavonoid substances, lead to similar conclusions which are considered elsewhere in this review.

The basic similarities in living cells of all kinds—plant and animal—are apparent in the very nature of living protoplasm itself and in the nature of the nutrient materials from which plants and animals derive energy and substance. The results of biochemical investigations of the past forty years have demonstrated that in the

cells of the most diverse types of organisms certain common reactions occur, and certain common substances and enzyme systems are present (Guzman Barron, 1943; Vickery, 1941). For the most part, the similarities referred to are most clearly recognized in the interrelated reactions involved in the transformations of sugars and simple amino acids. In the heterotrophic organisms these reactions follow the breakdown of ingested sugars, proteins, fats, etc., into simpler fragments which then form the common pool of carbon compounds from which more elaborate structures are later derived. In the higher plants, with which this review is primarily concerned, the raw materials of synthesis are provided by photosynthesis and by the absorption of inorganic ions from dilute solutions surrounding the roots. The striking similarities which exist between many of the cellular processes of organisms, such as yeasts, bacteria and animals on the one hand, and photosynthesizing plants on the other, must be clearly recognized, since they offer adequate justification for suggestions that an enzymatic mechanism known to operate in, say, a bacterial cell, may be involved, at least until we have evidence to the contrary, to account for a synthetic step in a plant in which detailed studies of cellular processes may not have been carried out.

It appears from what is known about cellular reactions in general and what has been discovered in recent years about the mechanism of photosynthesis, that a function of the photosynthetic process is to establish the stockpile of three- and four-carbon atom compounds which can enter into the metabolic cycles leading to carbohydrates, amino acids and the multiplicity of compounds which go to make up the organized individual.

It follows from these considerations that if one examines the cellular processes of the plant at some point after the photosynthetic fixation of carbon dioxide has been accomplished, there are few fundamental differences between the metabolic activities of photosynthesizing organisms and heterotrophic organisms. The differences that then arise, superimposed upon the early transformations of simple trioses, sugars, keto acids, etc., are the result of processes unique first to particular organisms and then to particular species, genera, families and phyla. It is then that genetic characteristics begin to manifest themselves and that enzymes or enzyme systems with unique functions must be sought.

The flavonoid substances of plants represent a group of com-

pounds well suited to serve as a basis for examining the range of complexity of basically related processes. They are, as a class, widespread in nature. Certain individual compounds are ubiquitous, being found throughout the plant kingdom. Certain types of compounds are equally widespread; but there are many classes with restricted distribution, frequently confined to one or two families of the higher plants. Finally, compounds are known which are unique to a single genus, species or individual.

A discussion of the biogenesis of these substances will most appropriately progress from the general to the particular. The "general" processes are those by means of which the products of photosynthesis are modified into the three-, six- and nine-carbon units which serve as the "common precursors" for the aromatic (C_6, C_6-C_3, C_6-C_3-C_6) end products. The "particular" processes are those by means of which differences in detailed structure of the final compounds are brought about, as in the formation of a group of anthocyanins or flavones of different hydroxylation patterns, or of different degrees and positions of attachment of sugar residues, etc. Since the chemical reactions through which the substances in the stockpile of intermediates are transformed may be assumed to be those of the kind well recognized in biochemistry and for the most part directly enzyme-mediated, it is appropriate to examine the nature of these reactions, and to review in particular the cellular transformations which involve the carbohydrates, trioses, simple hydroxy acids and keto acids. These may be regarded as the initial stages of processes whose later and more elaborate details are the ultimate concern of this review.

THE NATURE OF THE CELLULAR REACTIONS

The intermediate metabolites in the glycolytic cycles are very reactive substances from the standpoint of the organic chemist. They include such types of compounds as aldehydes; α- and β-keto acids; ketones; α-hydroxy acids and α-hydroxy ketones; α,β-unsaturated acids; carbonyl compounds; alcohols; and the α-amino acids which are in dynamic equilibrium with some of these. Enzymatically-mediated changes involving these groupings may be broadly divided into two classes (Geissman, 1949*b*): those involving acid-base catalyzed condensations and cleavages; and those involving oxidative changes, usually a dehydrogenation of one sub-

strate and a simultaneous reduction of another. The non-oxidative enzyme reactions of particular importance to the present discussion are those in which carbon-carbon bonds are formed and broken. Three types of reactions of this sort appear to be of special significance:

(*a*) *β*-Carboxylation. The condensation of carbon dioxide with a methylene group activated by (i.e., in the alpha-position to) a carbonyl group has been shown to be an important means of CO_2-fixation in higher plants. Examples of this reaction are the carboxylation of pyruvic acid and *α*-ketoglutaric acid:

$$CH_3-CO-COOH + CO_2 \rightleftharpoons HOOC-CH_2-CO-COOH \qquad (1)$$

$$\begin{array}{l} COOH \\ | \\ CH_2-CH_2-CO-COOH \end{array} + CO_2 \rightleftharpoons \begin{array}{l} COOH \\ | \\ CH_2-CH-CO-COOH \\ \quad\quad | \\ \quad\quad COOH \end{array} \qquad (2)$$

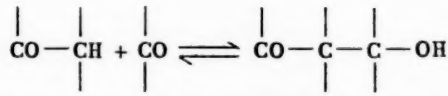
The coupling of these reactions with reduction to malic and isocitric acids, respectively, is indicative of their role in the metabolism of the di- and tricarboxylic acids of the citric acid cycle. It has long been known that in animal tissues the incorporation of carbon dioxide proceeds through an initial *β*-carboxylation. In higher plants the photosynthetic mechanism affords another route for carbon dioxide fixation.

(*b*) Aldol condensation. The importance of condensations of the aldol type in phytosynthesis has been discussed by Robinson (1917) who has suggested that reactions of this type play a major role in the syntheses of alkaloids and other kinds of compounds in plants. The aldol condensation may assume many forms; these differ in detail, but may be represented in the most general way by the following expression:

$$X-\underset{|}{\overset{|}{C}}H + \underset{|}{\overset{|}{C}}=O \rightleftharpoons X-\underset{|}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}-OH \qquad (3)$$

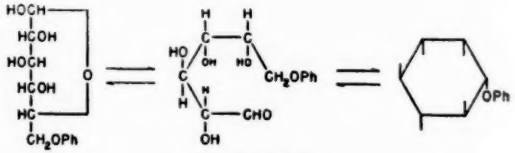
The necessary conditions for this reaction are an acidic ("active") carbon-linked hydrogen atom and a sufficiently reactive carbonyl group to which addition may take place. The "activation" of

the α-hydrogen atom is ordinarily achieved by the presence of a suitable group X (in the above equation). This is in most cases a carbonyl group, so that the generalized equation may be written as



(4)

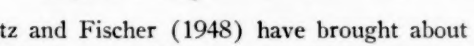
In biological systems aldol-like carbon-carbon bonding has been proposed in cases in which, if such a reaction indeed occurs, other kinds of activation must be present. For example, Fischer (1944–5) has suggested the biogenesis of meso-inositol by a cyclization of glucose-6-phosphate by what is clearly a condensation of the aldol type *:



D-glucose-6-phosphate

(5)

In this formulation the acidity of the hydrogen atom of the 6-methylene group is enhanced by the phosphate grouping, making possible an initial ionization of the following sort †



(6)

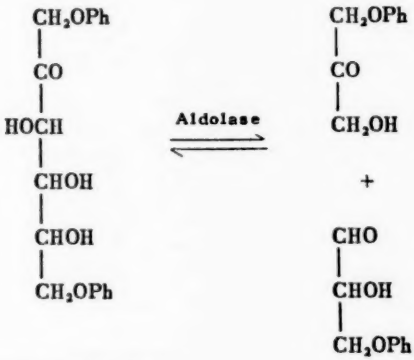
Grosheintz and Fischer (1948) have brought about a cyclization to a cyclitol of a sugar derivative in which a nitro group plays the role assigned to the phosphate grouping in equation 5. If the analogy suggested between cellular cyclization and the in vitro

* In this and the other equations and formulas in this review the phosphate grouping is represented by the symbol "OPh". This is done to avoid the necessity for being explicit about the state of ionization of the grouping, and to avoid the unsatisfactory representation of the group in the unionized form, $-OPO(OH)_2$.

† The use of the symbol B: for a generalized base is both convenient and necessary. The exact identity of such a species is not always known, particularly in biological systems involving enzyme participation. It might be, for example, water, hydroxyl ion or the enzyme protein (Geissman, 1949*b*). It is clear, moreover, that the degree of activation (i. e., the "acidity" of the proton to be removed) will be of importance in determining how strong a base is needed to produce a signicant ionization according to equation 6.

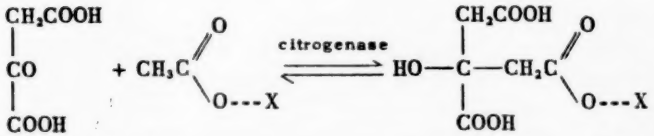
reaction exists, a new importance is attached to the process of phosphorylation in the cell. It must be pointed out, however, that although the kind of activating effect shown by the α-nitro group is well known, evidence as to a similar activation of a methylene group by the phosphate grouping is lacking.

The known examples of cellular aldol condensations, while not numerous, include reactions of the most fundamental importance in metabolic processes. The two most conspicuous of these are the reversible dismutation of fructose-1,6-diphosphate into two molecules of triose phosphate (Stumpf, 1948, 1950; Twefik and Stumpf, 1949), and the condensation of oxaloacetic acid with acetic acid (or a related two-carbon-atom fragment (Lipmann, 1946)) to yield citric acid. The occurrence of the latter reaction in plants may be inferred from the observations that have been made (Bonner and Bonner, 1948) on the relationship between carbon dioxide assimilation and the organic acid content of succulent plants.



(7)

fructose-1,6-diphosphate
(acyclic form)



(8)

The first of these reactions is an aldol condensation of the typical kind. The second deserves special attention, since it demon-

strates the activation of a methylene group (the methyl group of acetic acid) in a manner which may be of importance in other metabolic reactions. The addition of acetic acid or acetate ion, as such, to the carbonyl group of oxaloacetic acid appears highly unlikely, since the structural requirements for methylenic activation are not found in the carboxylate ion.

The reaction

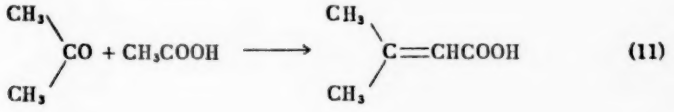
$$CH_3COO^- + B: \rightleftharpoons (:CH_2COO)^{2-} + BH^+ \qquad (9)$$

is improbable on energetic grounds. It is necessary to destroy or neutralize the highly inactivating resonance of the carboxylate moiety in order to make possible the ionization of the proton from the α-methyl group. In the laboratory this result is accomplished by working with the acid chloride or anhydride (as in the α-halogenation of fatty acids, or in the Perkin condensation) or the ester (as in the Claisen and Dieckmann reactions). In the cell the same purpose appears to be accomplished by the formation of a mixed acetic-phosphoric anhydride (Lipmann, 1946):

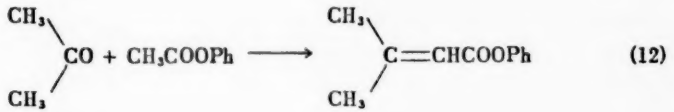
$$CH_3C(=O)-OPh + :B \rightleftharpoons (:CH_2C(=O)-OPh)^- + BH^+ \qquad (10)$$

Condensations of the aldol type may be assumed with reasonable assurance to be of wide occurrence in cellular processes, since many metabolic intermediates are known which have the proper structural features for their participation in such reactions. The stockpile of synthetic intermediates derived from photosynthesis, sugar and amino acid metabolism, and the tricarboxylic acid cycle contains substances peculiarly constituted to engage in reactions of the aldol type. α-Keto acids contain both a reactive carbonyl group and a reactive methylene group, and appear to play a central role in synthetic processes by virtue of their relationships to unsaturated acids (cis-aconitic, fumaric), α-hydroxy acids (malic, isocitric) and α-amino acids (alanine, aspartic, glutamic acids). Aldol condensations involving β-keto acids occupy an important place in theories of alkaloid biogenesis. Indeed, the activity of the methylene group when flanked by carbonyl and carboxyl groups is so enhanced that the mediation of specific enzymes need not be assumed to account for condensation reactions involving β-keto acids. The presence of β-keto acids in plants can only be inferred, since their instability (loss of CO_2) and their great reactivity would make their isolation difficult. The formation of the

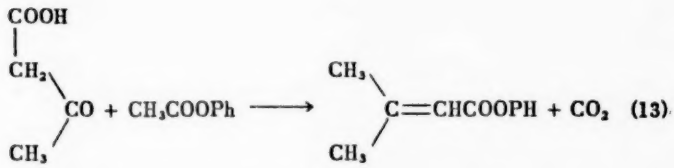
simplest member of the series, acetoacetic acid, in guayule has been suggested by Bonner (1949) who has offered a plausible mechanism for rubber synthesis by an aldol-like condensation between acetic acid and the acetone derived from acetoacetic acid by decarboxylation. That this reaction (equation 11) or its equivalent (equation 12 or 13)



(11)



(12)



(13)

may represent an important phytosynthetic process is an attractive possibility. The demonstration by Schöpf (Schöpf and Thierfelder, 1935; Schöpf et al., 1937) and others that β-keto acids can participate in vitro in condensation reactions which lead to alkaloids known to occur in plants offers support to the main features of such a proposal.

(*c*) Acyloin condensation. Condensations of the acyloin type cannot, on the basis of available evidence, be regarded as important reactions in higher plants, but they cannot be disregarded as possible synthetic processes. The reaction, represented by

$$R{-}CHO + R{-}CHO \longrightarrow R{\cdot}CHOH{\cdot}CO{\cdot}R \qquad (14)$$

is typified by the laboratory preparation of benzoin by the action of potassium cyanide on benzaldehyde:

$$C_6H_5CHO \xrightarrow{KCN} C_6H_5CHOH{\cdot}CO{\cdot}C_6H_5 \qquad (15)$$

An enzyme, "carboligase" (Neuberg and Hirsch, 1921; Hofmann, 1931; Stepanow and Kusin, 1930*a* and *b*, 1931, 1934; Silverman and Workman, 1941), capable of carrying out reactions of

this kind, has been claimed to exist in animal and plant tissues, but its identity is still in question (Dirscherl and Schöllig 1938; Tomiyasu, 1942). The well-established experimental observations are that when an aldehyde, for example, benzaldehyde, is added to fermenting yeast or certain plant tissues (notably leguminous seeds), a mixed benzoin is formed:

$$C_6H_5CHO + (CH_3CHO) \longrightarrow C_6H_5 \cdot CHOH \cdot CO \cdot CH_3 \qquad (16)$$

The bracketed acetaldehyde molecule may in actuality be pyruvic acid, which under the influence of carboxylase yields acetaldehyde. This acetaldehyde has been called " nascent ", but it seems best to avoid the use of such an indefinite term and to adopt the alternative suggestion that in the process of decarboxylation of pyruvic acid, the intermediate derived by the loss of CO_2 reacts, not with a proton- or hydrogen-donor to give acetaldehyde, but with the added aldehyde to give the acyloin. The reaction might be then written

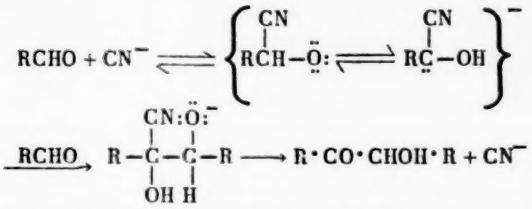
$$\begin{array}{l} \diagdown \\ \diagup \end{array}\!\!C{=}O + \begin{array}{l} | \\ CO \cdot COOH \end{array} \longrightarrow \begin{array}{l} \diagdown \\ \diagup \end{array}\!\!\begin{array}{c} | \\ C \\ | \\ OH \end{array}\!\!-\begin{array}{l} | \\ CO \end{array} + CO_2 \qquad (17)$$

It has been shown that enzyme preparations from animal tissues can catalyze the general reaction

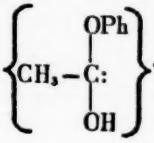
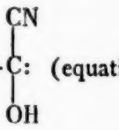
$$RCHO + (\text{respiring tissue}) \longrightarrow RCHOH \cdot CO \cdot CH_3 \qquad (18)$$

where R = CH_3, $CH_3CH{=}CH{-}$, $CH_3CH_2{-}$, $CH_3CH_2CH_2{-}$. Green et al. (1941) have also shown that α-keto glutarate can be decarboxylated to succinic half-aldehyde ($HOOC \cdot CH_2CH_2 \cdot CHO$), but no suggestion was made that carboligase-like reactions of this fragment follow its formation. The carboligase-like activity of bacteria is considered to be due to an enzyme system different from yeast carboxylase, since inorganic phosphate is required for the former but not for the latter.

The necessity for phosphate ion in the " carboligase " reaction is reminiscent of the suggestion of Fischer (1944–5) that the phosphate group serves as an " activating " group in the conversion of glucose to inositol. The role of cyanide ion in the benzoin condensation is regarded as that of an activating group which labilizes the hydrogen of the intermediate resulting from the addition of cyanide ion to the formyl group.



(19)

The addition of phosphoric acid to the carbonyl group of pyruvic acid could lead to an intermediate which upon loss of CO_2 would yield the highly nucleophilic species  . The resemblance of this to  (equation 19) is evident.

Even if phosphate can serve as an activating group having some of the "negative group" characteristics of the nitro and cyano groups, it is probable that such an activation would be confined to reactions directly mediated by enzymes, since phosphate does not appear to show such properties in in vitro experiments.

NON-ENZYMATIC SYNTHETIC PROCESSES

It has already been stated that the "small" molecules which take part in the interrelated reactions of photosynthesis, carbohydrate and amino acid metabolism, etc. are peculiarly constituted to show a high degree of activity in synthetic transformations. The role of enzymes in catalyzing these transformations is undoubtedly a dominant one, since the final compounds found in plants are usually, although not invariably, optically active when this is structurally permissible. However, Mannich (1928), in a discussion of the synthesis of alkaloids in plants, pointed out that "mild methods must be sought which, without the use of 'brutal' reactions, lead to complicated bases from simple starting materials". He continues: "It does not seem right to me to attempt to explain the astonishing chemical syntheses in plants only

through the wonderful action of enzymes. One must at least seek to find chemical processes which, without the action of enzymes, make intelligible the formation of alkaloids in the organism".

Experimental evidence exists to show that non-enzymatic reactions between highly reactive intermediates may play an important role in synthesis in higher plants. Henze and Müller (Henze, 1930; Henze and Müller, 1931) observed that methyl glyoxal and acetoacetic acid condense in aqueous solution at room temperature to give hexan-3-ol-2,5-dione.

$$CH_3COCHO + \underset{\underset{\displaystyle COOH}{|}}{CH_2COCH_3} \longrightarrow \underset{\underset{\displaystyle OH}{|}}{CH_3COCH}—CH_2COCH_3 \qquad (20)$$

Extension of this synthesis showed that it is general for aldehydes and β-keto acids; the following reactions were shown to proceed to give fair yields of the products indicated:

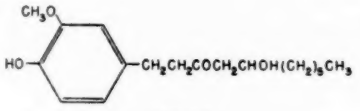
$$C_6H_5CHO + C_6H_5COCH_2COOH \longrightarrow C_6H_5CHOH \cdot CH_2COC_6H_5 \qquad (21)$$

$$C_6H_5CHO + HOOCCH_2COCH_2COOH \longrightarrow C_6H_5CHOHCH_2CO \cdot CH_2CHOHC_6H_5 \qquad (22)$$

$$R \cdot CHO + HOOCCH_2CO \cdot COOH \longrightarrow RCHOH \cdot CH_2CO \cdot COOH \qquad (23)$$

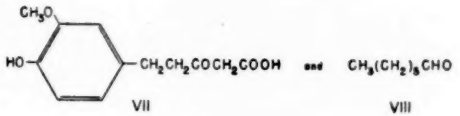
(R = phenyl, anisyl, vanillyl, 3,4-dihydroxyphenyl.)

While the most fruitful extension of this kind of reaction was found to lie in the field of alkaloids, its possible application to non-nitrogenous plant constituents is illustrated by a plausible synthesis of gingerol



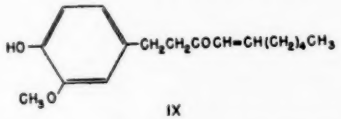
gingerol

from



VII VIII

The occurrence of the β-keto acid in the plant may be reasonably inferred from the presence in the same plant of both gingerol and gingerone, the methyl ketone derived by decarboxylation of (VII). Also present in the same plant is shogaol (IX)



IX

the synthesis of which may be inferred to take place in a similar way. The reactions of β-keto acids with aldehydes are further examples of the aldol condensation. The readiness with which they take place in the absence of special catalysts, such as enzymes or strong acids and bases, is attributable in large part to the pronounced activity of the doubly-activated (by carbonyl and carboxyl) methylene group.

Recent evidence indicates that in animal tissues fatty acid oxidation proceeds through successive β-oxidations followed by removal of two-carbon atom fragments. Although comparable evidence is lacking in the case of the higher plants (but *cf.* p. 149), the participation of the tricarboxylic acid cycle in the overall metabolism of the fatty acids, coupled with the importance of this cycle in plants, suggests that the postulation of the occurrence in plants of the β-oxidation of fatty acids is a reasonable one. It has been pointed out above that the widespread occurrence of the —$COCH_3$ unit in plant products strongly suggests the —$CO \cdot CH_2COOH$ precursor.

The enzymatic origins of aldehydes, with which β-keto acids may react, and which are widely distributed in plants (Rabinowitch, 1935, p. 249; Klein, 1932), may lie in such well-known processes as the decarboxylation of α-keto acids (Sumner and Somers, 1947, p. 319), the oxidation of alcohols by an alcohol dehydrogenase (Valdiquié and Bouyssou, 1946*a, b;* Kolesnikov, 1948; Clagett, Tolbert and Burris, 1949; Davidson, 1949*a*), and the degradation of α-amino acids through the successive action of amino acid decarboxylase and amine oxidase. The presence of the latter two enzymes in plants is not well established, although both types have been reported in germinating leguminous seeds (Werle and Pechmann, 1949). The ability of plants to produce aldehydes from α-amino acids has a high degree of plausibility in view of the suc-

cess of theories of alkaloid biogenesis, in which aldehydes play conspicuous roles, in accounting for the main features of alkaloid formation in plants, in allowing successful predictions of alkaloid structures as guides in chemical structure proofs, and in suggesting the brilliant in vitro syntheses of alkaloids under conditions simulating those prevailing in the living cell.

OXIDIZING ENZYMES

Plants are known to contain enzymes capable of oxidizing α-hydroxymonocarboxylic acids to α-keto acids (Clagett et al., 1949; Tolbert et al., 1949), hexoses and pentoses to the corresponding -onic acids (Miyake and Kurasawa, 1942; Sisakyan and Chamova, 1949), alcohols to aldehydes and formic acid to carbon dioxide (Davidson, 1949*a*, *b*), as well as the better known oxidative enzymes of the tricarboxylic acid cycle. The presence in bacteria, yeasts and fungi of oxidizing enzymes of other kinds, such as those which bring about the extensive changes in oxidation level which lead to such compounds as the lower aliphatic fatty acids, oxidize carbohydrates to ketosaccharonic acids, etc., allow the speculative inference that plants also possess still undiscovered mechanisms of oxidation and reduction which at the present time can be recognized only by the formation of end products differing markedly in oxidation level from the carbohydrate materials from which they are ultimately derived. The presence in certain plants of *n*-heptane and *n*-nonane, at the one extreme, and in others of flavones hydroxylated in seven of the possible ten positions, at the other, is evidence of the operation of powerful reducing and oxidizing systems in the cell. Such processes are exceptional, however, and it is best to be cautious in assuming the general availability of oxidizing and reducing enzymes of such unusual capacities, or of unique but experimentally still undiscovered types, in biogenetical speculations. There are always several possible (on paper) synthetic routes to a given result; the use of the well established facts of cellular metabolism cannot serve to select the correct route, but only to select the more probable from the less probable of the often numerous possible routes to a desired end product.

(To Be Concluded in the March Issue)

Future Contents of

THE BOTANICAL REVIEW

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Fungal Carotenoids	T. W. Goodwin *The University, Liverpool, England*
The Characeae — Their Value and Their Taxonomy	R. D. Wood *Rhode Island State College*
Plant Disease Control with Antibiotics	H. W. Anderson & David Gottlieb *University of Illinois*
The Histochemical Localization of Enzymes in Vascular Plants	D. S. Van Fleet *University of Missouri*
Southern Swamps and Marshes	W. T. Penfound *University of Oklahoma*
Chemical Regulation of Sexual Processes in the Thallophytes	John R. Raper *University of Chicago*
Placentation in Angiosperms	V. Puri *Meerut College, India*
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